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Identifying a Core Outcome Set for Cardiac Arrest Effectiveness Trials

by

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A thesis submitted in fulfilment of the requirements for the degree
of Doctor of Philosophy

University of Warwick

Division of Health Sciences, Warwick Medical School

September 2016

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List of acronyms:

ADL: Activities of Daily Living

AHA: American Heart Association

BI: Barthel Index

CA: Cardiac arrest

CDS: Core Domain Set

COMS: Core Outcome Measurement Set

COS: Core Outcome Set

COSCA: Core Outcome Set for Cardiac Arrest effectiveness trials

CRAG: Clinical Research Ambassador Group

COMET: Core Outcome Measures in Effectiveness Trials

CO-STAR: Core Outcome Set-STAndards for Reporting

CPC: Cerebral Performance Category

CPR: Cardiopulmonary Resuscitation

CTD-ILD: Connective Tissue Disease Related Interstitial Lung Disease

CVD: Cardiovascular disease

EQ-5D: EuroQol 5 Dimensions

ERC: European Resuscitation Council

GRADE: Grading of Recommendations Assessment, Development and Evaluation

GOS: Glasgow outcome score

GT: Grounded theory

HADS: Hospital Anxiety and Depression Scale

HEFT: Heart of England NHS Foundation Trust

HRQoL- Health Related Quality of

HUI-3: Health Utilities Index 3

ICD: Implantable Cardioverter Defibrillator

ICF: The International Classification of Functioning, Disability and Health

ICHOM: International Consortium for Health Outcomes Measurement

ILCOR: International Liaison Committee on Resuscitation

IPA: Interpretative Phenomenological Analysis

IPF: Idiopathic Pulmonary Fibrosis

ITD: Impedance Threshold Device

JDM: Juvenile Dermatomyositis

JSLE: Juvenile Systemic Lupus Erythematosus

mRS- modified Rankin scale

MMSE: Mini Mental State Examination

NGT: Nominal Group Technique

OMERACT: Outcome Measures in Rheumatology

OPC: Overall performance category

PARAMEDIC: Pre-hospital Randomised Assessment of a Mechanical Compression Device in Cardiac Arrest

PPI: Patient and Public Involvement

PRP: Patient Research Partner

PROMs: Patient Reported Outcome Measures

RA: Rheumatoid arthritis

RCT: Randomised Controlled Trial

ROSC: Return of Spontaneous Circulation

SF-12: Short form 12

SF-36: Short form 36

STEMI: ST Elevation Myocardial Infarction

TTM: Targeted temperature management

US FDA: United States Food and Drug Administration

VF: Ventricular fibrillation

WHO: World Health Organisation

Acknowledgements

I would like to thank my supervisors Kirstie Haywood and Gavin Perkins for their endless support and guidance, whom without this thesis would not have been possible.

I would like to thank the participants of this study for kindly giving up their time and support, to share their experiences and views informing this research.

I would like to thank some individuals who have contributed to this study: Teresa Melody; Keith Couper; Deborah Biggerstaff; Stephanie Tierney; Jonathan Bengner; Maaert Castren; Judith Finn; Kenneth Spearpoint; Jerry Nolan; Steve Brett; Vinay Nadkarni; Andrew Clarey and members of the Clinical Research Ambassador Group.

Finally, I would like to thank my family and friends who have been extremely supportive and understanding throughout my PhD. I dedicate this thesis to my Grandfather, Dr Dennis Ernest Mackley Evans.

Declaration

This thesis is submitted to the University of Warwick in support of my application for the degree of Doctor of Philosophy. It has been composed by myself and no parts have been submitted in any previous application for any degree.

The work presented (including data generated and data analysis) was carried out by myself.

Chapter 3 of this thesis has been published in the Journal resuscitation by the author: Whitehead, L., Perkins, G. D., Clarey, A. and Haywood, K. L. (2015) 'A systematic review of the outcomes reported in cardiac arrest clinical trials: The need for a core outcome set', Resuscitation, 88C, pp. 150-157.

Abstract

Cardiac arrest research seeks to improve survival rates and the quality of patient survival, but the comparability of research is limited by heterogeneous outcome reporting. The Core Outcome Set for Cardiac Arrest effectiveness trials (COSCA) study sought to identify the most important outcome domains that should be reported as minimum across all cardiac arrest effectiveness trials as part of a core outcome set (COS).

Multiple perspectives were sought across COS development to ensure relevance. Potential outcome domains for COS inclusion were identified in: a systematic review of outcomes reported in published randomised controlled trials (RCTs) and interviews with survivors of cardiac arrest and their partners to understand the health outcomes that really matter. Consensus on the most important outcome domains was achieved in: an international modified Delphi survey and an international consensus meeting.

Great heterogeneity (164 outcomes) was reported across current RCTs, failing to capture a number of outcomes important to cardiac arrest survivors identified in interviews. Across 2 rounds of ranking and rating exercise 48 outcome domains (18 health domains across 5 time points) were scored on their importance in the modified Delphi survey. Subsequently, 30 outcome domains were further discussed at a face to face consensus meeting.

Three core outcome domains were defined: survival to hospital discharge/30 days, neurological outcome at hospital discharge/30 days and health related quality of life (HRQoL) within 1 year. Preliminary guidance on appropriate assessment tools were made but further evidence and understanding of the most appropriate measurement tools is required. Implementation of the defined COS has the potential to improve outcome reporting across cardiac arrest effectiveness trials, aiding the comparison of findings through homogenous outcome reporting and ensuring the most important outcome domains to key stakeholders are reported.

Chapter 1: The Measurement of Health Outcome and Cardiac Arrest

1.1. Introduction

This chapter provides an overview of the measurement of health in general and an introduction to cardiac arrest research, providing a context for the work that follows. Section 1.2 describes the measurement of health, exploring why and how health is measured. In section 1.3 the importance of outcome assessment in clinical trials and steps towards improving outcome reporting through the development of core outcome sets is explored. Cardiac arrest, the impact on survivors, and the present status of outcome reporting in this population is discussed in section 1.4. Section 1.5 describes the foundation for the empirical work that follows - the development of a Core Outcome Set for Cardiac Arrest effectiveness trials (COSCA). The chapter concludes with the aims and objective of this thesis and a summary of the thesis structure.

Subsequent chapters will describe the COSCA study. Chapter 2 will describe the methodological approaches and specific methods considered in the development of a COS for cardiac arrest effectiveness trials, providing the methodological underpinning and justification of methods selected for chapters 3-6. Subsequent chapters will provide specific details about selected approaches, the data collection and analysis.

Chapter 3 describes a systematic review of outcome reporting in published cardiac arrest randomised controlled trials, highlighting the significant heterogeneity in reporting and the limited assessment of the perspective of survivors. Chapter 4 describes a qualitative exploration with survivors of

cardiac arrest and their partners, seeking to better understand their lived experience and the outcomes from healthcare that are most important.

Chapters 5 and 6 detail the steps taken towards engaging with international stakeholders towards achieving consensus on the outcome domains to include in the COS. Chapter 5 describes a two round, international, online modified-Delphi survey of healthcare professionals/researchers and patients/partners, during which participants were asked to prioritise outcome domains for inclusion in the COS. Chapter 6 details an international multi-stakeholder consensus meeting, where the final decision on the core domain set was achieved and measurement tools for the core outcome measurement set were explored. The content of the COS will be described.

Chapter 7 will bring together the findings from chapters 3-6 summarising the findings of the COSCA study and describing the implications for both cardiac arrest research and core outcome set development. This study provides a detailed and transparent account of the co-construction of a core outcome set for cardiac research, supporting a greater transparency in outcome reporting and ensuring the inclusion of core outcomes that have relevance and value to a range of key stakeholders. The importance of including the long-term and patient-derived assessment of health-related quality of life in cardiac arrest research will be introduced.

1.2. Measuring health

In this section the importance of health measurement will be discussed and key terms will be defined. Different approaches to measuring health will be described, including several classification systems for outcome measurement and taxonomies of measurement.

Definitions of health and health outcome

In order to measure health, it must be defined first. In 1946 the World Health Organisation (WHO) defined health as:

“a state of complete physical, mental and social well-being and not merely the absence of disease and infirmity,” (WHO, 1946).

To expand on this definition, physical health considers the functional ability of body organs and systems, mental health considers an individual's ability to deal with factors of daily life and social health refers to a person's interactions with other people (Warwick-Booth et al., 2012).

A criticism of this definition is the use of the word 'complete' because the majority of the population would be unable to achieve complete well-being (Huber et al., 2011). This flaw has become more apparent with changes in patterns of health resulting from advances in health care. Health has been previously described as two eras, firstly the fight against communicable diseases and secondly the era of chronic diseases (Breslow, 2006). Both these concepts of health are evident today but it has been acknowledged that we are in the third era of health with a growing focus on the population living longer with high expectations quality of life.

The International Consortium for Health Outcomes Measurement (ICHOM) define health outcome as:

“The results people care about most when seeking treatment, including functional improvement and the ability to live normal, productive lives.”

(<http://www.ichom.org/why-we-do-it/> cited 27.08.16)

Why is health measured?

Health is measured seeking to quantify health outcome, detecting changes to health for a number of purposes (Krousel-Wood, 1999). Health measurement in clinical practice and research such as blood tests, scans and questionnaires can determine the most suitable treatments, monitor patients and inform decision making (Black, 2013, Hausman, 2015). Measurement can provide evidence on the effectiveness of current standard care and new interventions influencing practice.

Successes and problems within healthcare may be identified through measuring health outcome, which can result in practice objectives being set or informing new research questions to improve healthcare provided (McDowell, 2006). Health measurement allows the comparison of quality between providers of health and also allows epidemiological comparisons (Black, 2013, Hausman, 2015). Economic analyses require health measurement and inform the allocation of resources (Hausman, 2015).

The National Health Service (NHS) in England aims to improve the health and wellbeing of patients, helping patients to get better through disease and illness, and stay as well as possible towards the end of life (Choices, 2008). To achieve these aims outcome frameworks are set, the current NHS Outcomes Framework (2016-2017) describes the following assessment domains:

1. Preventing people from dying prematurely.
2. Enhancing the quality of life for people with long term conditions.
3. Helping people to recover from episodes of ill health or following injury.
4. Ensuring that people have a positive experience of care.
5. Treating and caring for people in a safe environment and protecting them from avoidable harm. (

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/513157/NHSOF_at_a_glance.pdf, cited on 20.06.16)

To assess whether these aims have been achieved, a range of health outcomes are measured.

When measuring health, two questions are considered: firstly, “what to measure,” which domains of health are important, and secondly, “how to measure,” choosing the most appropriate method to assess outcome domains (Stucki et al., 2007). How to measure outcomes is a field that is evolving with the development of new measurement tools. These concepts

are addressed in the next sections, with classification systems considering 'what to measure', followed by 'how to measure' and taxonomies of health measurement describing different approaches to how to measure health.

Classification systems

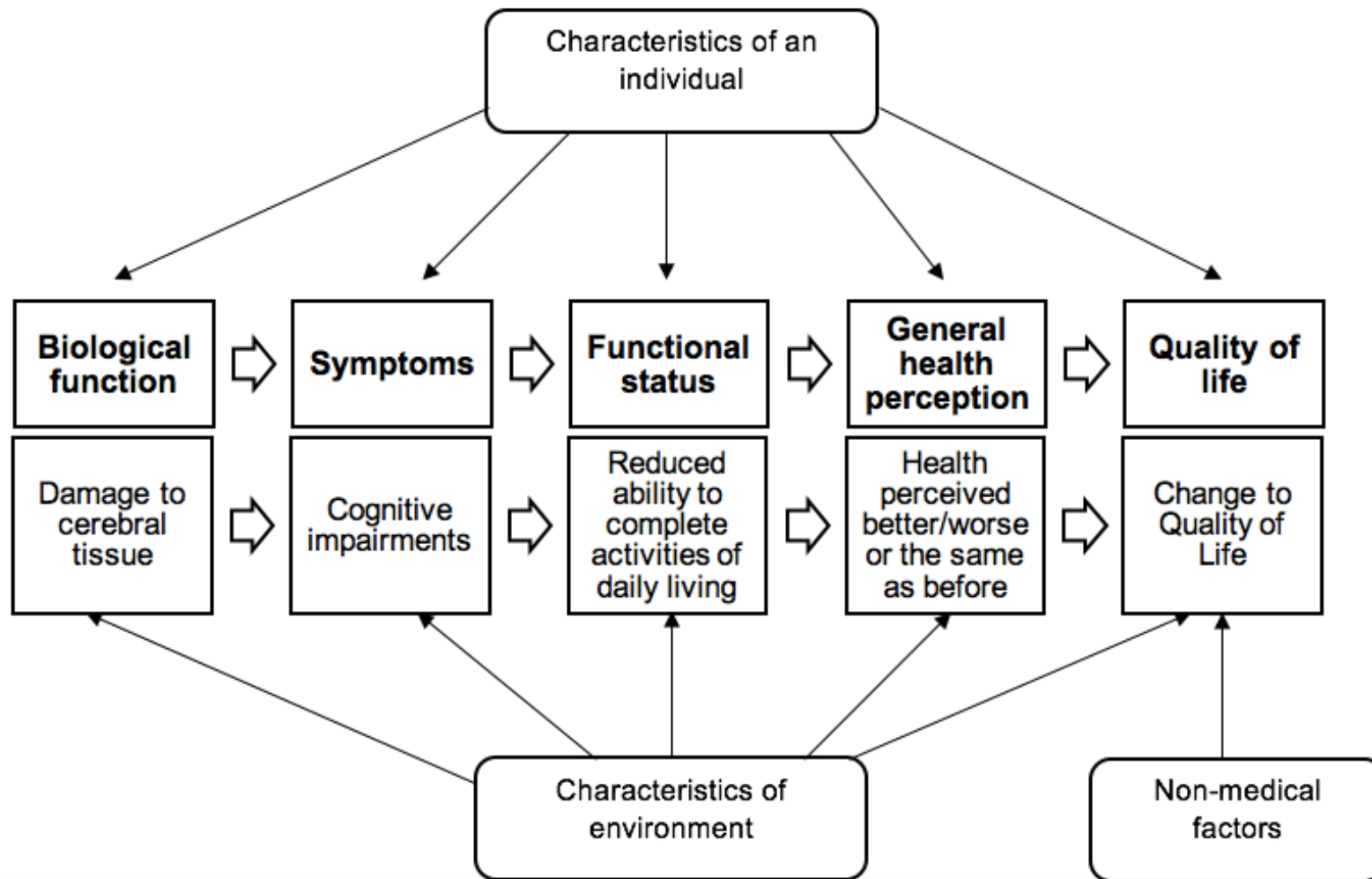
The measurement of health is complex, and should measure outcomes that are relevant to a range of different stakeholders including patients, health professionals and service providers (Haywood, 2010). A number of classification frameworks are available which seek to clarify the different concepts of health that can be assessed. Three widely referenced frameworks include: 1) the Wilson and Cleary Model of Health Related Quality of Life (Wilson and Cleary, 1995); 2) the International Classification of Functioning, disability and health (ICF) (WHO, 2001); and 3) the Outcome Measures in Rheumatology (OMERACT) Filter 2.0 (Boers et al., 2014c).

The Wilson and Cleary Model of Health Related Quality of Life (Wilson and Cleary, 1995)

In 1995 Wilson and Cleary proposed a classification system of health outcome, modelling Health Related Quality of Life (Wilson and Cleary, 1995). Outcomes are classified in five levels on a continuum of complexity: biological and physiological factors, symptoms, functioning, general health perception and overall quality of life. The framework is described within the context of causal factors such as support available and personal motivation. Figure 1.1 illustrates the framework describing health that may be experienced by a cardiac arrest survivor (Wilson and Cleary, 1995).

Biological and physiological factors describe measurement at a cellular, organ or organ system level, for example cerebral blood marker tests (Wilson and Cleary, 1995). Symptoms shift the focus to an organism as a whole and are categorised as physical psychophysical and psychological. Functioning describes the ability to perform tasks. Integration of these levels occurs influencing general health perceptions and our overall quality of life.

Figure 1.1: Wilson and Cleary model of Health Related Quality of Life in the context of a cardiac arrest survivor.



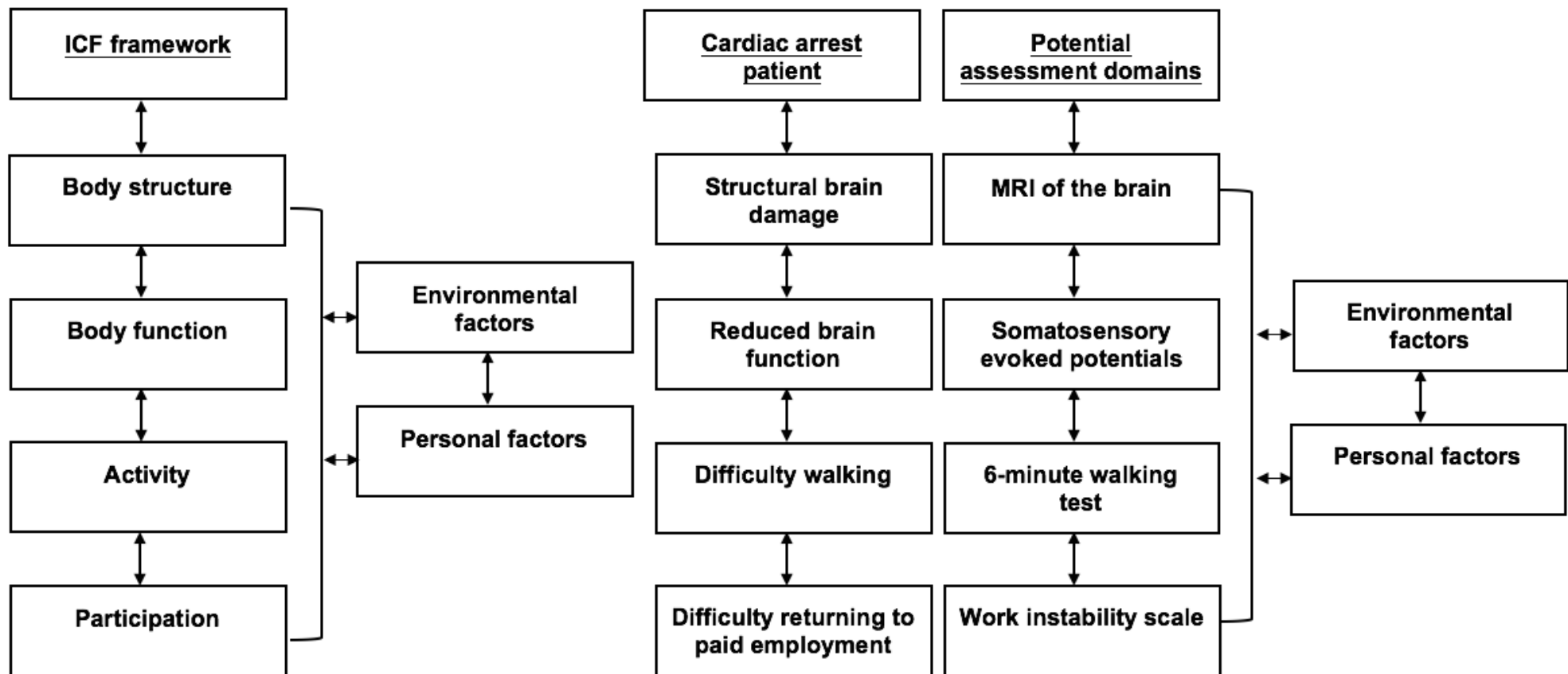
The International Classification of Functioning, disability and Health (ICF)(WHO, 2001)

The International Classification of Functioning, Disability and Health (ICF) (WHO, 2001) endorsed by World Health Organisation (WHO) members includes health and health-related domains. These domains include the components of functioning and disability; body structure, body function, activities and participation, but also contextual factors incorporating environmental and personal factors. Prior to revision the ICF framework was formerly the International Classification of Impairment, Disability and Handicap (ICIDH1) (Organization, 1980). The current ICF classification framework incorporates disability which has previously been treated as a separate component of health (Kostanjsek, 2011).

Figure 1.2 illustrates examples of outcomes within the ICF framework for a cardiac arrest patient with a hypoxic brain injury, demonstrating how the different factors of the framework influence health condition and other factors. In the ICF classification the domain of body function and structure refers to the anatomy and physiology of the body. Examples of measurement from body structure and function include: an (MRI) of the brain to indicate any change to brain structure and somatosensory evoked potentials to assess brain function. The health domain of activities focuses on the ability of an individual to execute tasks, for example after a cardiac arrest a patient may find walking difficult and their functioning may be assessed by a 6-minute walk test. Participation considers an individual's ability to take part in their normal life situations (roles and activities) including paid employment

which may be assessed by the work instability scale. Environmental factors are those that are beyond persons control and our dependant on our environment for example our economic background, religion or family. Personal factors include those such as gender, race and age (Jette, 2006).

Figure 1.2: The International Classification of Functioning, disability and Health (ICF) framework, with examples presented within the setting of a cardiac arrest patient.



***The Outcome Measures in Rheumatology (OMERACT) Filter 2.0
(Boers et al., 2014c)***

The Outcome Measures in Rheumatology (OMERACT), reviewed available outcome frameworks considering the suitability of application in core outcome set development (Idzerda et al., 2014). A Core Outcome Set (COS) seeks to standardise outcome measurement across clinical trials in specific healthcare areas and are discussed in greater detail in section 1.3.

The review explored the following frameworks: The World Health Organization conceptual framework of health (WHO, 1946); The Five D's (discomfort, disability, drug toxicity, dollar cost and death) (Fries et al., 1980); The International Classification of Functioning, disability and Health (ICF) (WHO, 2001); Patient-Reported Outcomes Measurement System (PROMIS) (Cella et al., 2007) and Porter's Outcome Hierarchy (Porter, 2010). The review concluded that none of the available frameworks including the ICF framework were immediately applicable to and able to improve the core outcome set development process within OMERACT.

Although previously recommended for its potential use in COS development (Stucki et al., 2007), the ICF framework focusses on functioning not considering all potential health outcomes, notably death which may be an expected health outcome in certain health areas (Idzerda et al., 2014). The review also concluded that: the PROMIS framework focussed on how to measure rather than what to measure, the Porter's hierarchy focused on the time point of measurement and the WHO and five D's frameworks were

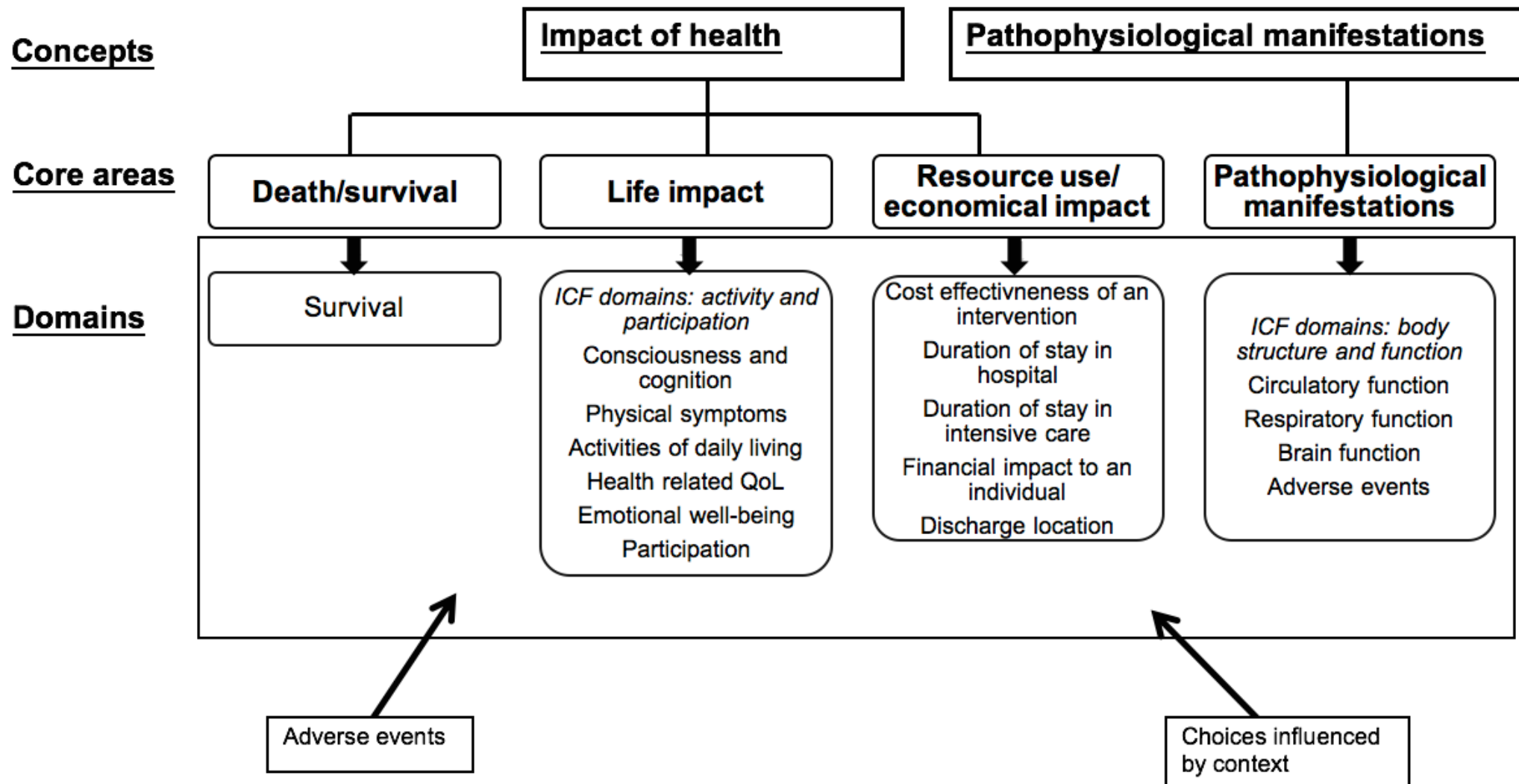
broad with limited methodological rigour (Idzerda et al., 2014). These factors limited the applicability of these frameworks in COS development which begins with seeking to define 'what' should be measured.

The critique of the existing frameworks informed the development of a new conceptual framework specifically designed to aid the development of core outcome sets (Idzerda et al., 2014). The OMERACT 2.0 filter conceptualises health and ill-health under two concepts: Impact of Health Conditions and Pathophysiological Manifestations (Boers et al., 2014c). The impact of health conditions includes three core areas: Death, Life Impact and Resource use/Economic Impact. Specific components of health domains are then described within each core area, providing an in-depth appreciation of the impact of health, ill-health and/or an intervention. Figure 1.3 illustrates the OMERACT 2.0 filter with examples of outcome domains from the field of cardiac arrest research and healthcare.

From the core area "Death", there may be a number of causes which may be disease or intervention specific. However, death may not be an expected outcome in all health areas and is absent from the ICF classification. The health domains considered within the core area "Life Impact" describe how life can be impacted as a result of a health condition, and include: activities and participatory issues that are considered within the ICF framework; quality of life; patient perception of health; and secondary impact on carers (Boers et al., 2014c). Domains considered within core area "Pathophysiological Manifestations" include: the ICF domains body structure and body function;

biomarkers; and surrogate markers. The framework explains adverse events should be reported to understand any harms of a treatment, and that contextual factors may be reported to further understand the outcomes of the study (Boers et al., 2014c).

Figure 1.3: OMERACT (Outcome Measures in Rheumatology) 2.0 Filter. Examples are listed in the context of the ICF framework and cardiac arrest patient population.



How is health measured?

In the 1800's Florence Nightingale classified her patients as 'relieved, unrelieved or dead,' (1863 cited in (Appleby et al., 2004)). Up until the early 1960's mortality rates were typically the only measurement of population health (Bergner, 1985). The measurement of health has developed greatly since then and here are various sources available to measure health and a variety of ways that these can be classified. Health can be measured by: physiological methods such as laboratory reports and exercise tests; by observations made by clinicians applying scales; or from the perspective of patients through questionnaires or patient reported outcome measures (McDowell, 2006).

In some health areas, health measurement has shifted from the reporting of traditional biomedical measures, which may not capture what is really important to patients, towards biopsychosocial assessments with an increase in the application of patient reported outcomes (Garratt et al., 2002, Appleby et al., 2004). Well-developed patient reported outcomes should reflect the outcomes that are most relevant to patients and their family (Patrick et al., 2007). The US Food and Drug Administration (FDA) have provided guidance for how PROMs should be developed and communicated to improve confidence in research findings from pharmaceutical industries. In the UK patient reported outcome measures are reported routinely in clinical practice in cataract surgery, varicose vein surgery, hernia repair and hip and knee surgery (Smith et al., 2005).

Taxonomy of measures of health

Different forms of health measurement can be classified and described by a number of characteristics. Health measurements can be broadly classified as either generic, specific, or individualised (Garratt et al., 2002, Haywood et al., 2012). Generic measures of health are not age, disease, population, or treatment specific, containing multiple concepts of health which are intended to have relevance to patients and the wider general population. Generic measures can be applied across a broad range of health conditions and patient populations. Moreover, population-based normative values can be calculated which supports data interpretation (Garratt et al., 2002).

Two classes of generic measures are defined: health profiles and utility measures. Health profiles measure important dimensions of health related quality of life, and utility measures consider preference of health states, and enable economical evaluations (Preedy and Watson, 2010). Examples of widely used generic measures include the Short form (36) Health Survey (SF-36) (Ware and Sherbourne, 1992) and the EuroQol 5 dimensions questionnaire (EQ-5D) (Rabin and de Charro, 2001).

Specific measures may be specific to a disease or illness (for example, heart failure: Minnesota Living With Heart Failure Questionnaire (MLHFQ) (Rector et al., 1987)), a population (for example, children: the Paediatric Quality of Life Questionnaire (PedsQL) (Varni et al., 1987)(<http://www.pedsq.org/>)), a symptom (for example, fatigue: Chalder Fatigue Scale (Chalder et al., 1993)), a described function (for example, basic activities of daily life: the

modified Rankin Scale (Bonita and Beaglehole, 1988)), or an intervention (for example, the Oxford Hip Score for considering hip replacement (Dawson et al., 1996, Garratt et al., 2002). Well-developed specific measures are likely to have improved item relevance to patients and clinicians than generic measurements, and hence have greater clinical appeal. Moreover, they are likely to be more responsive to important changes in health (Wiebe et al., 2003).

Unlike more traditional measures where respondents are expected to answer all listed questions, irrespective of personal relevance, individualised measures allow patients to report issues that are of personal importance. Examples include the Schedule for the Evaluation of Individual Quality of Life (SEIQoL)(O'Boyle et al., 1993) and the Patient Generated Index (Ruta et al., 1994). Although they tend to be highly relevant at an individual level with good content validity, they often have poor self-completion rates (Haywood et al., 2003).

The application of health measurement

Measures of health outcome are increasingly applied across a range of settings including: routine practice (Marshall et al., 2006); in disease registries (Gräsner et al., 2011, Sleat et al., 2011); audit (Nolan et al., 2014) and clinical research including clinical trials (Brundage et al., 2011).

Routine practice

Health is measured in routine clinical practice to monitor the health of patients. Measurement can inform diagnosis, prognosis and the impact and suitability of chosen treatment (Sackett, 1997). The measurement of health in routine practice patients will not know whether their treatment is having the appropriate effect, whether they can adapt their lifestyle to reduce any known health risks. Measuring health promotes and improvement in health status (Davies and Crombie, 1997).

Disease registries and audit

In registries, data is systematically collected for a predefined purpose such as to monitor and understand care systems or to study the epidemiology of a particular population (Arts et al., 2002). Clinical audit is similar to registry health measurement but focusses on the evaluation of a health service, understanding the success of care and to identify where improvements can be made. Audit aims to maintain and improve quality in healthcare resulting in improved patient outcome and satisfaction, whilst improving cost effectiveness of a system (Bowling, 2014).

Clinical research

Clinical research is important to determining the impact of a treatment and its effectiveness in comparison to current available treatments (Friedman et al., 2010). Research can provide information on the effectiveness of treatments and the evaluation whether the benefits outweigh the costs determining their appropriateness.

It is important to understand the overall impact of a treatment to patients' health in addition to the target therapeutic area including any unintended side effects. Understanding the overall impact to health is important when considering the most appropriate treatments with patients (Hausman, 2015).

Clinical research can be conducted in several different designs each with variable levels of evidence (Grimes and Schulz, 2002). Experimental studies included randomised controlled and non-randomised controlled trials. Observational studies with a control group are analytical and can be cohort, case-controlled or cross-sectional. Observational studies with a comparator group are descriptive.

1.3. Clinical trials and Core Outcome Sets

Pragmatic, effectiveness trials are designed to assess the effectiveness of healthcare interventions in routine clinical practice (Godwin et al., 2003, Macefield et al., 2013). Selected outcomes provide quantified evidence of the relative benefits or harms of an intervention in clinical trials. Outcome selection is therefore an important step in trial design (Macefield et al., 2013, Stanley, 2007), with some suggesting, "*Clinical trials are only as credible as their endpoints,*" (Tugwell and Boers, 1993). It is a requirement in research to pre-define study outcomes (primary and secondary), with primary outcomes informing sample size calculations (Stanley, 2007).

The Enhancing the Quality and Transparency of Health Research (EQUATOR) network (<http://www.equator-network.org>) brings together a number reporting guidance documents, to support interpretation of clinical trials and minimise risk of biases in reporting. For example the CONSORT recommendations (Consolidated Standards of Reporting Trials) describe a standardised approach to presenting trial findings, promoting reporting completeness and transparency to allow interpretation and appraisal (Moher et al., 2012, Schulz et al., 2011, Calvert et al., 2013).

SPIRIT recommendations are available to inform the report of Standard Protocol Items. Within the SPIRIT recommendations outcome details including specific measurement variables, analysis methods and time point of assessment for the disclosure of primary, secondary and other outcomes (Chan et al., 2013). Since 2005 The International Committee of Medical Journal Editors have made it a requirement that details of clinical trials are registered on an open database before they are published, this includes the disclosure of the primary and secondary outcomes (DeAngelis et al., 2004).

Despite such recommendations a number challenges of outcome reporting in clinical trials remain, including heterogeneous outcome reporting, biases and research waste, these challenges are discussed (Glasziou et al., 2014).

Challenges of trial outcome reporting and biases

Heterogeneous outcome reporting

The comparison of interventions can be problematic because of the variety and inconsistencies in outcome reporting (Clarke, 2007, Williamson et al., 2012b). Problems resulting from inconsistent outcome reporting are often highlighted when completing systematic reviews and meta-analyses (Williamson et al., 2012a). Meta-analyses are viewed as the highest level of research evidence bringing together study populations and to help draw conclusions from results explaining the impact of an intervention (Egger et al., 1997, Koroshetz, 2015), but if trials are not assessing the same outcomes it is difficult to synthesise studies.

The impact of outcome reporting on systematic reviews was highlighted in a review of 2535 systematic reviews from The Cochrane Library (Clarke et al., 2007). The review explored the extent that Cochrane reviews recommend the need for further research and suggestions made regarding research outcome reporting, 51.9% of reviews included a suggestion that outcome measured should be more appropriate, standardised or as assessed in the review. In addition to this the 10 most accessed and 9 most cited Cochrane reviews in 2009 (Tovey, 2010) all reported challenges associated with inconsistent outcome reporting (Williamson et al., 2012b).

Outcome reporting bias

Outcome reporting bias is the publication of a selection of outcomes originally reported, selected on the basis of the results (Hutton and

Williamson, 2000). Smith and colleagues reviewed outcome reporting across 788 Cochrane reviews, identifying 6,127 pre-specified outcomes, 37% of these were not reported (Smith et al., 2015). This form of bias is an issue for both the results of individual trials and questions the validity of subsequent systematic reviews and meta-analyses. When adjusted for the risk outcome reporting bias a review of 42 meta-analyses found, 26% of the reviews overestimated the treatment effect by 20% or more (Kirkham et al., 2010).

Further to this, in the Outcome Reporting Bias in Trials (ORBIT), 143 studies included in 40 Cochrane reviews were explored for data completeness. In 18% of these studies more than 50% of patient data was missing for the primary outcome, indicating outcome reporting bias (Kirkham et al., 2013b).

Publication bias

Publication bias occurs when investigators, reviewers and editors decisions to submit or accept articles for publication are influenced based on the significance or direction of study findings (Dickersin, 1990). Evidence reports that published studies are more likely to be positive and statistically significant ($p < 0.05$) than unpublished studies (Dickersin and Min, 1993, Easterbrook et al., 1991). This raises ethical issues for those that have participated in research contributing to research waste and patient care influenced by research evidence. The non-publication of results may lead data synthesis to produce misleading conclusions and potentially over estimating benefits or hiding potential harms of treatments (Smith, 1980).

Research waste

Global biomedical research involves millions of participants and billions of dollars, despite these high investments there are concerns that research is not reaching its full potential causing research waste (Macleod et al., 2014). Chalmers and Glasziou estimate that the loss of research investment may be as high as 85% (Chalmers and Glasziou, 2009).

There are a number of contributors to research waste: Firstly, research should seek to answer high priority questions that are relevant to both clinicians and patients; assesses important outcomes, and involve stakeholders in setting the research agendas (Chalmers and Glasziou, 2009, Chalmers et al., 2014). Secondly, inappropriate study design and selected methods can contribute to research waste (Chalmers and Glasziou, 2009). Thirdly, the under publication of complete study findings (publication bias) and biased publications (outcome reporting biases) have a role in research waste.

Core Outcome Sets

To address the many challenges associated with poor outcome reporting explored above, the concept of defining core outcome sets for clinical trials has been introduced (Clarke, 2007, Williamson et al., 2011, Tugwell et al., 2007).

A core outcome set is:

“a standardised set of outcomes which should be measured and reported, as a minimum, in all effectiveness trials for a specific health area”

(Gargon et al., 2014).

Trialists are not restricted to reporting outcomes from the COS, with additional outcomes expected to be reported alongside a COS.

Moreover, it is not a requirement the study primary outcome is from the COS, although a COS may assist primary outcome selection (Clarke and Williamson, 2015). If well-developed, core outcome sets seek to overcome problems associated with outcome reporting by reducing the heterogeneity in outcome reporting, promoting transparent outcome reporting and increasing the relevance of outcomes to all stakeholders.

Terminology of Core Outcome Sets

A Core Outcome Set (COS) has two sub-components:

- First, the Core Domain Set (CDS) – describes the minimum number of outcome domains to be included in the COS. The CDS defines ‘what’ to measure or which outcome domains to be measured (Boers et al., 2014c).
- Second, the Core Outcome Measurement Set (COMS) – describes methods of assessment, or specific outcome measures which will be used to assess the core outcome domains. The COMS defines ‘how’ outcome domains will be measured (Boers et al., 2014c).

Advantages and limitations of COS

The advantages and challenges of core outcome sets have been explored in a survey of 45 Cochrane co-ordinating editors (Kirkham et al., 2013b).

Advantages identified included: reducing the heterogeneity in outcome reporting; aiding systematic reviews and meta-analysis; improving interpretation and guidance; outcomes reported are more likely to be appropriate; aiding new study design and reducing outcome reporting bias, through transparent outcome reporting.

However, challenges associated with COS development included: greater clarity in the steps required to both identify which outcomes should be assessed and how these should be assessed; the potential absence of measurement tools for important outcome domains and the preliminary nature of COS requiring an updating process (Kirkham et al., 2013b). One concern of editors was how to promote implementation and encourage trialists to use core outcome sets. A separate group of trialists highlighted a limitation of core outcome sets in the field of asthma, currently the COMET database lists 14 COS for asthma studies which can cause confusion over which COS to use implement (Keener, 2014).

History of Core Outcome Set Development

Early approaches to standardisation of outcome reporting

One the earliest reports of research which sought to achieve a standardised approach to outcome reporting across cancer trials to increase the

comparability of research findings is reported by the World Health Organisation (WHO) outcomes for Cancer group (Miller et al., 1981).

Although specific methods adopted by the authors were not detailed and hence a critique of the approach is not possible, two meetings were held: the first in 1977 and the second in 1979 with 19 and 23 international participants respectively. Participants were representatives from a number of organisations including the European Organisation for Research on Treatment on Cancer (EORTC) and the International Union Against Cancer. However the type of stakeholders is unclear with no report of patient participation (Miller et al., 1981). A minimum data set to be collected and reported for cancer clinical trials which included the following key was recommended including: patient data; tumour data; treatment reporting; toxicity reporting; response to treatment; reoccurrence and results of therapy.

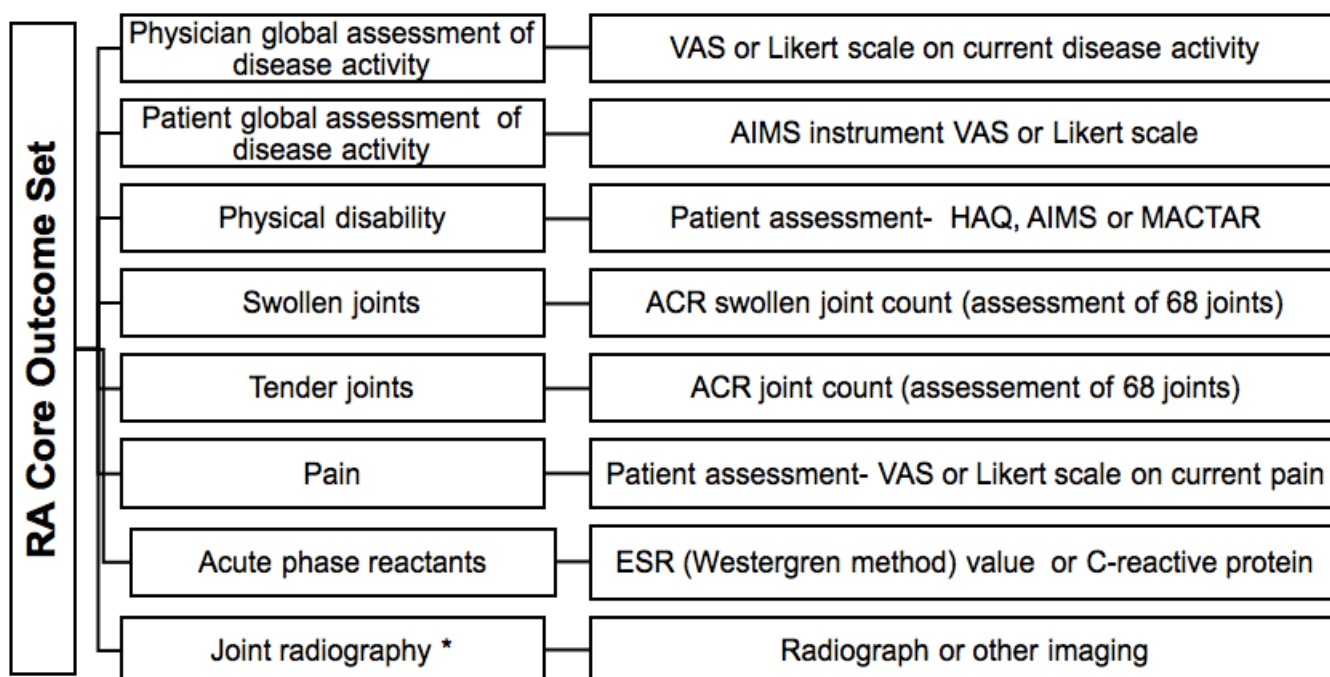
The field of Rheumatology has been aware of the challenges of heterogeneous outcome reporting for more than 30 years (Wright, 1981, Bombardier et al., 1982, Symmons and Dawes, 1988, Scott et al., 1989, Felson, 1992, Scott et al., 1991) which resulted in the establishment of the Outcome Measures in Rheumatology (OMERACT) initiative in 1992 (<http://www.omeract.org/>). The first meeting in 1992 was initiated by a discussion between trialists who highlighted the reporting of different outcomes in European and North American rheumatoid arthritis trials, resulting in difficulty comparing the results of trials and including studies in meta-analyses (Tugwell et al., 2007). The meeting was attended by a total of

92 experienced clinicians, clinical investigators, representatives from industry and regulatory agencies from an international background, however patients were absent from this process (Boers et al., 1994).

The meeting sought to: 1) identify outcomes that should be reported as a minimum across all rheumatoid arthritis (RA) trials; 2) explore the similarities and discrepancies between clinicians and clinical trialists with regards to the outcomes they judged as important for RA clinical trials; and 3) to review the usefulness of aggregate measures (indices) (Tugwell et al., 2007). Meeting discussion content was informed by two previous recommendations from the American College of Rheumatology (ACR), European League Against Rheumatism (EULAR) (Felson, 1992, Felson et al., 1993, Scott et al., 1992). Delegates participated in large group plenary sessions and small group discussions with voting exercises before and after discussions.

The meeting concluded with interactive voting and although the level at which consensus was confirmed was not reported. 'Consensus' was achieved for a seven-domain core outcome set (eight domains for studies longer than a year), pain; patient global assessment; physical disability; swollen joints; tender joints; acute phase reactants; physician global assessment; and joint radiography (studies longer than a year) (Boers et al., 1994). The results were approved at a further meeting in the same year, where Committee on Outcome Measures in Rheumatoid Arthritis Clinical Trials of the ACR recommended how to best assess core outcomes (Figure 1.4) (Boers et al., 1994, Felson et al., 1993).

Figure 1.4: Rheumatoid arthritis Core Outcome Set from the first OMERACT meeting (Boers et al., 1994, Felson et al., 1993).



Footnote: Abbreviations: ACR: American College of Rheumatology; AIMS: arthritis impact scale; ESR: erythrocyte sedimentation rate; HAQ: health assessment questionnaire; MACTAR: McMaster and Toronto Arthritis patient preference disability questionnaire and VAS: Visual analogue scale

Since the first OMERACT meeting in 1992, core outcome sets have been developed and ratified at further WHO meetings on a wide range of rheumatology trial areas including: osteoarthritis (Bellamy et al., 1997); ankylosing spondylitis (van der Heijde et al., 1997); psoriasis/psoriatic arthritis (Gladman et al., 2007); and acute gout (Schumacher et al., 2009).

Once the question of ‘what’ to measure has been answered, the consideration of ‘how’ to measure outcomes selected for COS inclusion is considered, defining a COMS. Outcome measures considered to assess core outcome domains are required to pass the OMERACT filter to be endorsed, components of the filter are: truth, discrimination and feasibility (Tugwell et al., 2007). Truth assesses the ability of the measure to assess what it proposes to, addressing the validity (face, content, construct and criterion) of the tool. Discrimination concerns the ability to differentiate between situations considering reliability and sensitivity. Feasibility considers the ease of application of the tool in practice which can be effected by constraints such as cost and time.

The OMERACT group has supported methodological advancement in the field of COS development and outcomes research more generally. In particular, it has been fundamental in the contribution of patients as research partners and participants in outcomes research (de Wit et al., 2014, Boers et al., 2015). Advancements in COS development will be discussed in chapter 2.

Core outcome set development beyond cancer and rheumatology

Since the first reporting of a COS is credited to Boers and colleagues in 1992 (Boers et al., 1994), there has been a steady growth in COS development and associated publications (Gargon et al., 2014). This increase in COS development is fuelled by the importance of data synthesis from clinical trials to inform evidence-based healthcare, the call for greater transparency in outcome reporting and the importance of reducing research waste (Williamson et al., 2012a). The importance of COS for clinical trials, and the growth in availability, was recognised in the establishment in 2010 of the Core Outcome Measures for Effectiveness Trials (COMET)-initiative, funded by the UK Medical Research Council (<http://www.comet-initiative.org/about/fundingandsupport> cited on 28/06/16).

A primary aim of COMET is to bring together relevant stakeholders, including researchers, health professionals, and patients, to facilitate the development of core outcome sets (Walker, 2010). The COMET initiative provides an online information resource for COS development and application, listing important COS related publications and a database of ongoing and completed COS. The COMET initiative database currently lists 813 references of planning ongoing and completed COS related researcher (<http://www.comet-initiative.org> cited on 9/06/16). The database is important to reducing the risk of COS duplication and can enable collaboration by listing ongoing and completed COS.

In 2012 the International Consortium for Health Outcomes Measurement (ICHOM) was founded to develop agreed sets of outcomes to use in clinical trials and practice, that reflect outcomes that matter most to patient (Kelley, 2015). ICHOM was founded by three groups: the Institute for strategy and competitiveness (Harvard Business School), The Boston Consulting Group and the Karolinska Institutet (<http://www.ichom.org/who-we-are/> cited on 16.05.16). ICHOM develops standardised set through a series of teleconferences followed by a survey completed by working group members including: patients; healthcare professionals, researchers, measurement experts and policy representatives from an international background (Kelley, 2015).

ICHOM reports to have developed 13 standardised sets that cover approximately 35% of global disease burden, these include: coronary artery disease (McNamara et al., 2015), stroke (Salinas et al., 2016) and advanced prostate cancer (Morgans et al., 2015) (<http://www.ichom.org/who-we-are/> cited on 16.05.16).

Core Outcome Set implementation

In order to see the potential benefits of core outcome sets they need to be implemented by trialists. However, there is limited guidance on how to address implementation and only a small number of studies have explored COS implementation.

An analysis of 350 RCT's explored the implementation of the COS for rheumatoid arthritis which was first published in 1994 (Kirkham et al., 2013a). RCTs were categorised into pre-outcome set publication (published up to 1994) and post-core outcome set publications (published 1994 and later). Reporting of the 7 (8 for studies with duration over a year) core outcome domains, was extracted and compared between time periods.

Studies were further categorised by intervention: pharmacological disease-modifying anti-rheumatic drugs/ slow-acting anti-rheumatic drug (DMARD/SAARD); symptom-modifying anti-rheumatic drugs (SMARD); glucocorticoids and biologics; and non-pharmacological interventions (alternative therapies; assistive technology; diet; exercise; rehabilitation and surgery).

Full COS reporting in the post-COS timeframe was low for exercise (0/3), surgical (0/3) and rehabilitation (1/40) interventions. COS uptake was high in biologic studies shorter than a year (26/28) and longer than a year (7/11). After COS publication DMARD/SAARD studies increased core outcome domain reporting increased from 27% (9/33) to 85% (7/20) and 25%(3/12) to 53% (9/17) in studies shorter and longer than a year respectively (Kirkham et al., 2013a). The authors concluded the findings suggest 60-70% of trialists are using the core outcome set in the field of rheumatoid arthritis, indicating that COS implementation can be successful increasing homogeneity in outcome reporting.

Subsequently, authors were contacted to explore why COS had not been implemented and 42/98 contactable authors responded to email correspondence. Fifteen respondents did not report all outcomes from the published COS, 11 of these authors were unaware of the COS at the time of study inception. Reasons for non-reporting of the COS of authors aware of the COS were: that studies had a safety focus (n=2), authors had forgotten to report all outcomes in the publication (n=1) and did not measure one outcome at a time when the COS had been developed but not published. 14 of the 15 trialists said that they would consider reporting all core outcomes in future studies (Kirkham et al., 2013a). This study indicates that for successful COS implementation dissemination is important to increase awareness and clarity.

Further to this, implementation of COS in axial spondyloarthritis patients has been investigated (Bautista-Molano et al., 2014). RCTs up to June 2013 and were categorised into two phases: a control phase (trials published up to 2 years after COS publication) and an implementation phase (trials published from 2 years after COS publication). Forty-eight control and fifty-one implementation studies were identified. No control studies included all core outcome domains and a fifth of implementation phase studies reported all core outcome domains (Bautista-Molano et al., 2014). Despite 20% further steps are required to improve implementation and the benefits of COS reporting in this field.

A recent review of the RCTs citing the COS from the Prevention of Fall

Network Europe (ProFaNE) has reported limited uptake, with only 1 of the 34 identified RCTs reporting all core domains (Copsey et al., 2016). Reporting of the five core outcome domains varied across the 34 RCTs: falls (94%), fall related injury (47%), psychological consequences (21%), health related quality of life (HRQoL) (24%) and physical activity (24%). A major limitation of this review is that it only considered studies aware and citing the COS, potentially over or under estimating the degree of COS implementation. Further steps are required to encourage successful COS implementation.

1.4. Cardiac arrest

Cardiac arrest is a sudden, life threatening condition defined by consensus by the International Liaison Committee on Resuscitation (ILCOR) as:

“Cardiac arrest is the cessation of cardiac mechanical activity as confirmed by the absence of signs of circulation.”

(Jacobs et al., 2004).

To overcome the physiology of cardiac arrest, cardiopulmonary resuscitation (CPR) is implemented to restore patients' life and functioning. Success resuscitation has been defined by authors as:

“to be cognitively unimpaired and with an acceptable quality of life, or to report no significant deterioration when compared to their pre-morbid state.”

(Bossaert et al., 2015).

Incidences and survival rates

Cardiovascular disease (CVD) is a huge burden to health, with CVD being accountable for approximately a third of deaths each year in the UK (Scarborough et al., 2010). It has been estimated that there are approximately 250,000 out-of-hospital cardiac arrest (OHCA) in Europe each year (Atwood et al., 2005) and emergency services attend 320,000 cardiac arrest each year in the United States (Mozaffarian et al., 2015). Survival rates from OHCA are both low and variable. A systematic review of international figures indicated lower survival rates in Asia (2.2%) in comparison to America (6%), Europe (9%) and Australia (11%)(Berdowski et al., 2010). High variation have been reported nationally, within the UK and US with survival to discharge reported as low as 2.2% up to 12% (Perkins and Cooke, 2012) and the 3.3-16.3%(Nichol et al., 2008) respectively.

Survival rates can be reported at different time points in the patient journey, once a return spontaneous circulation is achieved it does not mean it will be sustained, with patients regaining a pulse at risk of re-arresting. In the UK variation in initial ROSC was seen in 13.3-26.7% of patients, indicating that more than half of those having an initial survival will not make it to hospital discharge (2.2-12%)(Perkins and Cooke, 2012). Survival rates from a cardiac arrest occurring in the hospital environment are slightly higher in the UK than they are out of hospital, with in-hospital cardiac arrest (IHCA) survival rates close to 20% (Nolan et al., 2014). The internationally variable yet low survival rates from cardiac arrest and high incidence is a concern and highlights a

need for more research in this patient population (Nichol et al., 2008, Becker et al., 1993, Perkins and Cooke, 2012, Sandroni et al., 2007).

Physiology of cardiac arrest

Cardiac arrest is an extremely serious health event, the heart stops beating and stops the blood flow around the body and the subsequent oxygenation of organ tissue. Chest compressions and ventilations are required to sustain blood flow and the supply of oxygen to tissue. Defibrillation is often required to restart the heart. Immediate CPR is essential increasing the chances and the quality of that survival (Cobb, 2007).

On patient arrival to hospital targeted temperature management is started. This evidence based advance in the care of cardiac arrest patients which has shown to reduce the cognitive implications of surviving a cardiac arrest (Nielsen et al., 2013, Arrich et al., 2016). Once resuscitated patients are at risk of post-resuscitation syndrome, this shows similarities to sepsis and from this knowledge there is hope that developments can be made in post resuscitation care in the future (Cerchiari, 2007). Disruptions to tissue metabolism resulting from ischemia and reperfusion can cause organ damage with the brain at the most noticeable risk (Negovsky, 1972) (Negovsky and Gurvitch, 1995).

To prevent a cardiac arrest occurring again treatment reflects the cause of the arrest. An Implantable Cardioverter Defibrillator (ICD) is fitted if rhythmicity of the heart was the cause. If the arrest was caused by a

restriction of blood flow to the heart a percutaneous coronary intervention (PCI) may be considered (Noc et al., 2007).

Impact of surviving a cardiac arrest

Resulting from neurological disturbances after cardiac arrest patients may be severely disabled and may be discharged to a long term nursing facility resulting in a major impact to their life. The degree of impact after cardiac arrest can be variable. Many patients may experience disruption to cognition such as memory and decision making skills with a reported 50% of cardiac arrest survivors experiencing disturbances to cognition (Moulaert et al., 2009).

A review of quality of life and other patient centred outcomes in the cardiac arrest field has recently been completed to determine whether the quality of survival after cardiac arrest is acceptable (Elliott et al., 2011). Varied findings were reported with: 46 studies were supportive of a positive outcome, 17 demonstrated neutral results and 7 studies reported a negative impact on outcome. However, these findings should be taken with caution as studies used generic HRQoL measurement tools, undefined questionnaires and basic clinician assessed measurement tools that are designed to assess neurological outcome and functional status (Elliott et al., 2011). Currently there are no specific health related quality of life measurement tool for the cardiac arrest population.

After cardiac arrest many survivors return to work and others may choose to take early retirement. A range of return to employment figures have been reported including as low as 13% (Lundgren-Nilsson et al., 2005) and as high as 78% (Kragholm et al., 2013) of cardiac arrest survivors returning to work within 1 year.

Measuring health in cardiac arrest

Disease registry and audit

The Utstein resuscitation registry template exists to support the uniform reporting of a data for cardiac arrest registries (Perkins et al., 2014). The most recent update to the guidelines reflect changes in technology, advances in resuscitation care and the need to capture the patients' perspective. Across the revisions the templates served the combined or individual population of out of hospital cardiac arrest (OHCA) and in hospital cardiac arrest (IHCA) patients, the first and most recent revision of the template has different templates for the different patient groups. The current template lists 23 core data elements and 30 supplementary elements across the five domains of: system, dispatch, patient, process and outcome (Perkins et al., 2014) (Appendix 1.1).

Despite the Utstein Resuscitation Registry template providing recommendations for data reporting there is heterogeneity in registry data collected internationally, reflecting differences in cultural views and capabilities of systems in different countries (Gräsner et al., 2011). A

retrospective analysis of registries from 13 countries, reported 61.9% of registries collected all core data variables (Nishiyama et al., 2008).

Recently a European Cardiac Arrest Registry (EuReCa) has been set up to allow the comparison of registry findings between different European countries, allowing for understanding of variability in survival rates and differences in care and population which could influence the way patients are treated (Gräsner et al., 2011). Initial comparisons of national registries from five countries indicated differences in registry structure and complexity, and variation in outcomes reported including whether registries reported the incidence of bystander CPR and the number of patients brought to hospital alive.

Clinical research

Despite the large proportion of cardiovascular deaths caused by cardiac arrest, when compared to myocardial infarction, stroke and heart failure there is a relatively small proportion of published randomised controlled trials focussed on cardiac arrest and resuscitation. This is highlighted in a study by Ornato and colleagues with only 177 resuscitation RCTs being identified using MEDLINE opposed to 7691, 3639 and 4108 for myocardial infarction, stroke and heart failure respectively (Ornato et al., 2010). Research in the field of cardiac arrest is important to improve survival and quality of survival of patient suffering cardiac arrest. Research in the cardiac arrest population is complex and faces challenges, particularly ethically due the unconscious state of the patient.

Clinical research influences routine care of cardiac arrest patients and since 2000, Consensus on Cardiopulmonary Resuscitation (CPR) Science with Treatment Recommendations (CoSTR) for treating cardiac arrest patients have been made (Nolan et al., 2015). These are evidence based guidelines which are reviewed every 5 years. International Liaison Committee on Resuscitation (ILCOR) taskforces prioritise and formulate research questions in the PICO format (Population Intervention Comparator and Outcome) (Higgins and Green, 2008). Using recommendations from the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Working Group evidence is evaluated to develop recommendations on the quality of evidence (high, moderate, low or very low) (Schünemann et al., 2009). Recommendations of care are classified as strong or weak with an overall assessment and statement (Nolan et al., 2015).

The current care guidelines emphasise the importance of a complete chain of survival to give patients the best chances of survival. This chain is made up of five stages; firstly the early recognition that the patient is in cardiac arrest and an early call for help, early good quality cardiopulmonary resuscitation, early defibrillation and post resuscitation care highlighting different potential areas to target in clinical research (Nolan et al., 2006).

There is no guidance available on which outcomes researchers should report in cardiac arrest trials. A meeting described by Becker and colleagues sought to identify a single primary outcome to report across trials of cardiac arrest therapies (Becker et al., 2011). A primary outcome is the most

important outcomes to a study and from which the study is powered on to complete analysis (Andrade, 2015). Over two days 61 clinical researchers (and 7 observers) engaged in face to face discussions focussed on: what are the most important outcomes, how they should be assessed and the cost associated with measurement (Becker et al., 2011). The meeting concluded that no single outcome could be the most important and reported across all trials in this field. Meeting conclusions suggested that the assessment of neurological functional outcome at 90 days is likely to be important to the majority of trials.

Developing a Core Outcome Set for Cardiac Arrest effectiveness trials

There is no COS developed for cardiac arrest research. Evidence of significant heterogeneity in outcome reporting in post resuscitation care has been reported (Trzeciak et al., 2009), alongside concerns about the heterogeneous nature of outcome reporting and its impact on data syntheses (Aung and Htay, 2005, Elliott et al., 2011, Moulaert et al., 2009). In addition to this ILCOR have highlighted that the evaluation of interventions is key to result in an improvement in patient outcome and that previous evaluations have been restricted due to inaccuracies in data collection which may be contributed by a lack of uniform reporting (Jacobs et al., 2004).

In addition to the issues surrounding heterogeneous outcome reporting, there is the need for research to have relevance to all key stakeholders.

Current research in cardiac arrest effectiveness trials is focusses on clinician assessment during patients' time in hospital, which may not include

assessment of the most important outcomes to survivors of cardiac arrest (Sawyer and Kurz, 2015, Whitehead et al., 2015, Haywood et al., 2014b).

There is a need for a core outcome set in cardiac arrest effectiveness trials to improve the homogeneity of outcome reporting, supporting easier comparison of trials and the inclusion of studies in systematic reviews and meta-analysis, subsequently reducing the potential for research waste. The inclusion of key stakeholders – including survivors of cardiac arrest and their partners, clinicians, health professionals and researchers; in the co-construction process will ensure that the range of potential outcome domains judged as important and relevant to key stakeholders will be considered for inclusion. This, in turn, should seek to improve the relevance and acceptability of the resulting COS, and hence the implementation in future clinical trials.

The scope of this core outcome set is to serve cardiac arrest effectiveness trials in adult out-of-hospital and in hospital cardiac arrest patients. At the time of COSCA study inception the scope of the study was analogous to the Utstein registry data reporting recommendations which considered both in and out of hospital cardiac arrest patients (Jacobs et al., 2004).

1.5. Aims and objectives

Research aim:

To develop an internationally endorsed, multiple perspective core outcome set for cardiac arrest effectiveness trials that has relevance to key stakeholders.

Research questions:

- 1.1 Which outcomes are currently reported in cardiac arrest randomised control trials?
- 1.2 Which outcomes really matter to patients who have survived a cardiac arrest?
- 1.3 Which outcomes do the survivors of cardiac arrest, their partners, clinicians, nurses and allied health professionals involved in the care of cardiac arrest patients, and/or research related to this population, think are the most important following cardiac arrest, and should be included in future clinical trials?

Chapter 2: Methodological considerations and methods for the COSCA study

2.1. Introduction

This chapter will provide an exploration of the methodological rationale behind the key components and considerations in COS development. The chapter will first provide an overview to COS development and approaches. Section 2.2 will describe four key methodological considerations, discussing available approaches and justification of selected methods for the COSCA study. Chapters 3-6 will include detail the specific considerations and approaches adopted with each stage of COS development.

2.1.1. Background to Core Outcome Set (COS) Development

Core Outcome Set Rationale

Core Outcome Sets seek to overcome a number of problems associated with current outcome reporting in health research trials described in chapter 1. The principal aim of a Core Outcome Set is to reduce heterogeneity in outcome reporting across trials in a particular health area, thus improving the consistency and comparability of research findings (Williamson et al., 2012b). To ensure that the final selection of outcome domains has relevance to key stakeholders - including patients, healthcare professionals and researchers, the process of developing a standardised set of outcomes requires broad consideration of many outcome domains that could be assessed in a trial (Williamson et al., 2012b)

Approaches to Core Outcome Set Development

Two key stages in COS development have been described: 1) Defining 'what' to measure – the Core Domain Set (CDS); and 2) Defining 'how' to measure - the Core Outcome Measurement Set (COMS) (Boers et al., 2014c, Williamson et al., 2012b). This thesis will focus on the first step, defining a Core Domain Set (CDS).

Good practice guidance for COS development does not currently exist and there is significant variation in the approaches adopted by many COS developers. A review of 198 studies (published 1981 to 2013) has explored methods applied to consider of outcomes reported in trials. Outcome selection is a stage of COS but the review was not exclusive to COS publications. The review was recently updated to include a further 29 studies (published prior to 2015) (Gorst et al., 2016).

The review and update highlighted significant variation in the methods adopted, poor reporting of and limited justification for the methods adopted. A lack of transparent reporting was illustrated, with 70% of studies failing to clearly define the population characteristics served by the COS and 53% failing to clearly define the intervention characteristics of the COS (Gargon et al., 2014, Gorst et al., 2016). The authors concluded that specific methodological guidance for COS development was required and standards for reporting should be developed (Gargon et al., 2014, Gorst et al., 2016).

In response, to the lack of transparency in reporting of methods completed in COS development the Core Outcome Set-STAndards for Reporting (CO-STAR) project was initiated, seeking to improve the transparency of outcome reporting but also increasing awareness of methodological considerations in COS development (Kirkham et al., 2015).

OMERACT, a group with an established track-record in COS development for rheumatological conditions, has recently detailed a 'step-by-step' approach to COS development (Boers et al., 2014c, Boers et al., 2015). This guidance was published after inception of the COSCA study. Guidance describes: following defining the scope of the COS any contextual factors need to be considered. Contextual factors are defined as variables that need to be reported to understand the study results but are not outcomes, for example the quality of CPR provided in the context of cardiac arrest (Boers et al., 2014c). Specific adverse events to be included in the COS should also be specified. Next a literature review of all reported domains (sub)domains and measurement instruments used to date is completed (Boers et al., 2015). This involves consideration of databases and search terms to identify all potential domains and instruments (Boers et al., 2015). Consultation occurs with multiple stakeholders to identify and missing domains, guidance of this stage is limited and is reported to occur in the form focus groups and surveys.

Identified outcome domains are then mapped to the OMERACT 2.0 filter framework. Consensus development of outcome domains to be included in a

core outcome set is achieved through: surveys, Delphi surveys, discussions outside and at OMERACT conferences. Often consensus is set at a level of 70% (Boers et al., 2015). A draft core domain set is agreed by the working group, further discussed and voted on at OMERACT conferences. Once a preliminary core domain set has been defined, a rigorous process takes place to assess the truthfulness, discriminability and feasibility of potential outcome measurement tools to include in a Core Outcome Measurement Set (COMS) (Boers et al., 2014c).

This guidance provides an overall structure for development of COS but lacks a methodological underpinning or detailed guidance of appropriate methods to apply. Currently consensus on the most appropriate methods to develop COS does not exist.

Developing the COSCA study

Given the lack of methodological debate or good practice guidance for COS development at the time of the initiation of the COSCA-initiative, reviews of current approaches (Gargon et al., 2014, Gorst et al., 2016), key OMERACT publications (Bellamy et al., 1997, Tugwell et al., 2007, Boers et al., 2014c, Bartlett et al., 2012, Mease et al., 2008), the OMERACT handbook (Boers et al., 2015), publications from the COMET management group (Sinha et al., 2011, Williamson et al., 2012b), and published COS articles (Schmitt et al., 2011, Harman et al., 2015, Potter et al., 2015a, Haywood et al., 2014a) provided crucial evidence informing the range of possible methods which were considered in development of the COSCA study.

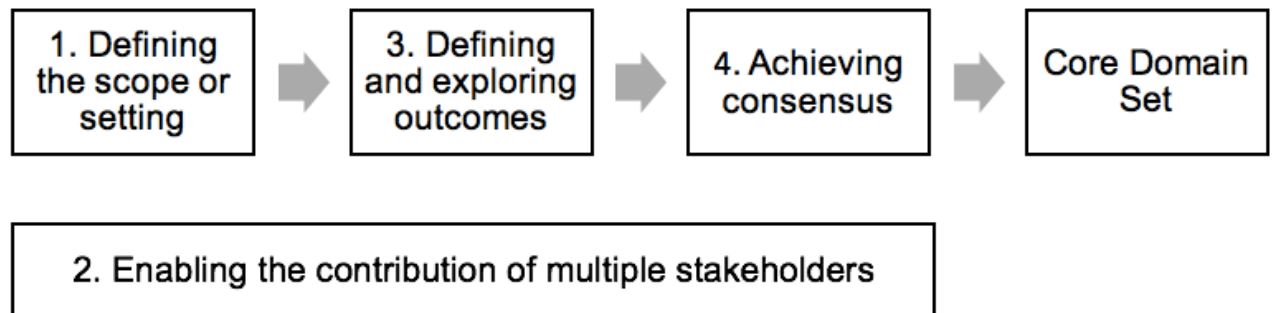
2.2. Methodological considerations

A COS is a consensus-derived, minimum number of key outcomes to be assessed in a specified situation, as defined by the perspective of relevant multiple stakeholders (Schmitt et al., 2015). There are a number of methodological considerations that have been described Including (Schmitt et al., 2015, Williamson et al., 2012b):

1. Defining the scope of the COS
2. Enabling the contribution of multiple stakeholders: as both participants and partners in the COS process
3. Defining and exploring outcomes: which outcomes should be considered for inclusion in the COS?
4. Achieving consensus: which outcomes are the most important and should be included in a COS? Achieving consensus on a global level.

In this section, the key theoretical underpinnings and constructive framework for COS development will be explored. For the purpose of this thesis, the following methodological considerations will be explored (Figure 2.1). Once COS have been developed there a three further considerations: reviewing and updating the COS, implementation of the COS and transparent dissemination of the COS (Williamson et al., 2012b).

Figure 2.1: Methodological considerations in Core Domain Set development.



2.2.1. Defining the scope of the Core Outcome Set

The initial step in Core Outcome Set development is defining the scope of the COS (Schmitt et al., 2015, Boers et al., 2015). There are a number of considerations to define the scope of studies served by the application of a COS, the first is the population served, this may include factors such as: disease and subgroups, disease progression and age group. The geographical scope and setting of outcome measurement should be defined, for example: different types of clinical trials, clinical practice or registry. In addition to these factors the types of interventions being compared should be described.

The scope of the COS relates to the PICO model of developing a research question where PICO is defined as: P-population, I-intervention, C-comparator/control and O-outcome. Defining the scope of a COS refers to the population, intervention and comparator (Boers et al., 2015)

(<http://www.comet->

[initiative.org/assets/downloads/Guidance_for_trialists.pdf](http://www.comet-initiative.org/assets/downloads/Guidance_for_trialists.pdf) cited cited

11.06.16)

and a COS seeks to define the outcome.

The COSCA study aims to define a COS for future cardiac arrest effectiveness trials of adult, out-of-hospital and in hospital cardiac arrest patients. The scope of the COSCA study includes effectiveness trials investigating interventions applied at the time point of arrest and during hospital stay.

2.2.2. Enabling the contribution of multiple stakeholders: as research partners or participants in the COS development

A growing body of evidence highlights how health outcomes (Staniszewska et al., 2012, Hewlett, 2003) and healthcare priorities (Tallon et al., 2000, Crowe et al., 2015) may differ between stakeholder groups – for example, between researchers, clinicians, the public and patients. These differences in views highlight the need to ensure the contribution of multiple stakeholder groups in COS development. A range of stakeholders can contribute to COS

development in different capacities as research partners or participants. For the purpose of these thesis we define research partners and participants:

- Research partners: Research partners, contribute to the study design and conduct, this is often described as 'involvement'. For example, research partners may be involved in the inception of a COS, the design of the methods conducted or the analysis of data collected.
- Research participants: Participation describes the contribution of stakeholders to data collected. For example, in COS development participants may contribute to qualitative methods in understanding important outcome domains and participating in consensus development methods, contributing their views on the most important outcomes.

Previously in COS development there has been a lack of transparency in how stakeholders, particularly patients and the public have contributed to COS development. This confusion has arisen due to a lack of detailed reporting, terminology used inconsistently, different forms of contribution being grouped together and stakeholders having multiple roles in COS development.

Within OMERACT PRPs are defined as:

“Persons with a relevant disease who operate as active research team members on an equal basis with professional researchers, adding to benefit of their experiential knowledge to a research project,”

(de Wit et al., 2011).

The term PRPs was adopted to distinguish between the role of patients as collaborative partners from those participating in qualitative methods and surveys (Boers et al., 2015). OMERACT refer to attendees of consensus conferences as partners, in this thesis this considered participation in a consensus method rather than involvement.

COMET have recently highlighted the different ways in which stakeholders can contribute to COS development, as partners and or participants (Young and Bagley, 2016), after concerns of the lack of transparency were raised at COMET workshops. COSCA steering members attended and contributed to this discussion point at two of the workshops (LW: Calgary, LW and KH: London). However, there does remain to be a lack of clarity to how qualitative data informing COS should be classified. The publication reports ‘patient involvement’ in a number of protocols describing qualitative interviews but no clear involvement of patient research partners in the study design (Harman et al., 2015, Keeley et al., 2015, Tong et al., 2015, Waters et al., 2014). In this thesis contribution to qualitative data on the importance of outcomes is considered as participation.

Both involvement and participation will be discussed in further detail, supported by examples in COS development. When discussing previous contribution to COS development an interpretation the nature of stakeholder contribution has been made on based on the methods authors describe.

2.2.2.1. Stakeholder involvement as research partners

It is important to have a management team representative of relevant stakeholders and including members with experience of outcomes research in COS development (Schmitt et al., 2015). There is increasing awareness that the involvement of patients and the public as research partners in research can benefit research. In 1996, National Institute for Health Research supported the establishment of the INVOLVE initiative to support patient involvement as research partners in NHS, public health and social care research (www.invo.org.uk, cited on 01.07.16).

INVOLVE describes patient and public involvement (PPI) as either research conducted 'with' or 'by' the public, including patients, their partners lay members and potentially future patients (Hayes et al., 2012). Three types of involvement are described: consultation, collaboration and user-controlled. Consultation describes discussing views with patient and public partners to inform decision making. Collaboration describes a shared role between patients and members of the public and the research team in decision making in the conduct of a study, for examples patient and public partners may collaborate with researchers in the production of study grant applications and dissemination documents. User-controlled involvement is

when patients and the public actively have a role in the direction and management of research, for example they may conduct research activities.

Patients first attended an OMERACT meeting in 1992, however the contribution of patients to the OMERACT COS development process has evolved over the years. Dual roles of patients are described: patients may be participants in research projects, for example, participating focus groups to inform data generation or consensus development methods; or, they may be patient research partners (PRP) with specific, defined and active collaborative roles within the core research team. OMERACT guidance requires a minimum of two patient research partners (PRP) per Working Group (Boers et al., 2015).

The potential benefits of PPI in COS development has resulted in the establishment of the People and Patient Participation, Involvement and Engagement (PoPPIE) group under the auspices of COMET (Bagley et al., 2015). To support the active participation of patients and the public in COS development, the group have co-produced a plain language guides for a summary of COS and Delphi survey processes (Bagley et al., 2015). These resources are available online however detail of the co-production process of document development is not reported (<http://www.comet-initiative.org/resources/PlainLanguageSummary> cited on 14.07.16)

2.2.2.2. Stakeholder participation as research

participants

A review of 198 studies choosing important health outcomes for trials reported a range of participants in the methods to select outcomes. The review reported stakeholder participants from the following groups with the reported incidence across the 198 studies: clinical experts (87%); public representatives (16%); non-clinical research experts (27%); authorities (20%); industry representatives (16%) and others (including ethicists and journal editors) (Gargon et al., 2014). Recent guidance from OMERACT supports the participation of reported stakeholders (Boers et al., 2015), with the addition of funders, healthcare policy groups, trial managers. Guidance described public representatives to include: patients, consumers, family members, care givers and advocacy groups.

Patient and public participation will be discussed in further detail and how multiple stakeholders can participate in COS development is described in sections 2.2.3 and 2.2.4.

Patient and public participants

There has been increasing awareness of the value of patients and public as participants across COS, with COS historically having participants predominately comprising representatives of employed professionals within healthcare and research (Gargon et al., 2014). Patients bring to research a different perspective to healthcare professionals and researchers, having the unique first-hand experience of disease and care (Hayes et al., 2012). It is

important that trials assess outcome domains that are meaningful to all stakeholders including patients.

The first report of patient participation in COS development was reported in 2002 during the 6th OMERACT meeting (Kirwan et al., 2003). From a total of 125 international delegates (from 17 countries), 11 of these were patients from 6 countries. The Patients' Perspective workshop was held with the aim of preparing evidence and arguments for the consideration of valid outcome domains from the patients' perspective for COS inclusion. From the workshop three areas of development were highlighted: 1) novel outcomes and approaches to assessment, 2) terminology and current knowledge and 3) the role of the patient. Since OMERACT 6 in 2002 patients have attended all subsequent meetings.

A recent evaluation of patient participation at OMERACT conferences between 2002-2010, a period where 58 patients had attended OMERACT conferences, sought evidence of the impact of patient participation (de Wit et al., 2014). The evaluation included a content analysis of OMERACT conference documents, publications and conference proceedings. In addition, 38 interviews were conducted at OMERACT 10 (2010, Malaysia) with 32 participants: 16 researchers, clinicians or industry representatives and 16 patients (8 new to OMERACT). Patient participants represented a variation of previous experience at OMERACT meetings, seven nationalities and a range of rheumatological conditions with a majority of rheumatoid arthritis (RA) patients (n=10).

The impact patient attendance and participation was defined across five categories: 1) widening the research agenda – in particular towards exploring newly identified outcome domains including: wellbeing, sleep disturbance, flare and fatigue (de Wit et al., 2013b, Kirwan et al., 2003); 2) ensuring that patient relevant outcomes were included in core outcome sets; 3) changing perspectives; 4) enhancing the content and relevance of patient reported outcome measures; and 5) changing the culture of OMERACT (de Wit et al., 2013b).

Fatigue is a well-illustrated example of how patient participation has impacted COS set development within OMERACT. Fatigue was absent from the original COS for rheumatoid arthritis COS developed at the first OMERACT meeting in 1992. Fatigue was discussed at OMERACT 3 (1996), a meeting with no patients attending (Newman, 1997), but fatigue was not considered for COS inclusion until its' importance to patients with RA was highlighted through qualitative explorations (Carr et al., 2003, Hewlett, 2003). Fatigue was discussed in depth at OMERACT 6 at the Patients' Perspective workshop, where patients first participated in OMERACT conferences (Kirwan et al., 2003). Subsequently fatigue was voted by the large majority (89%) of 70 participants (including 20 patients) to be included in the COS for RA at OMERACT 8 (Kirwan et al., 2007).

Beyond OMERACT, a review of 198 studies which considered the selection of outcome domains for studies stated that 18% of studies 'involved' members of the public (Gargon et al., 2014). When exploring evidence

further it was concluded that authors of this review used the term 'involved' to describe public participation. However, across studies reporting contribution of patients and the public 39% failed to transparently report the stage of participation. An update of this review including 29 further studies described and increase in public participation to 22% across the total studies reviewed (Gorst et al., 2016). In addition to this 90% of 72 ongoing trials listed in the COMET database have the public participating at some stage of COS development.

Challenges of patient participation

Despite the benefits of including patient and public as participants, this can raise a number of challenges, particularly in healthcare areas where integration of stakeholder participants is not an established concept. Initial concerns related to the ability of patients to understand the methodological components of COS development, and to provide a representative voice for the population as a whole (de Wit et al., 2014). However, as participation and confidence of patient participants has grown the benefit of their contribution was recognised. Moreover, the presence of patients at meetings acted as a constant reminder of why the research was important.

Qualitative interviews with 16 patients attending OMERACT 10 were conducted to understand their experience of participation at face to face meetings, 8 were attending an OMERACT conference for their first time (de Wit et al., 2013a). Patients new to the conference felt privileged to be invited and were unsure what to expect from the meeting. For patients the meeting

was both physically and mentally tiring which could have been facilitated with further individual support. Some patients were unsure if they had made a valuable contribution, but found the meeting a valuable learning experience and explained they would have more contribute at subsequent meetings (de Wit et al., 2013c).

This data synthesis highlighted facilitators and barriers to patient participation in the OMERACT conferences, highlighting considerations specific to face to face meetings. Factors that facilitate the process included: strong leadership, individual support, conference design and facilitative style (de Wit et al., 2013a). Barriers to patient participation included: overwhelming and overburdening participants, scepticism from professional participants, a lack of divergent views and experience and the differences in education and nativity between participants.

2.2.2.3. Stakeholder contribution from an international setting

The importance of achieving global consensus across international settings is supported by the COMET-initiative (Williamson et al., 2012b) with the argument that it enhances the comparability of research evidence across international settings. Moreover, whilst supporting the importance of international consensus, OMERACT have highlighted potential international differences which may influence the choice of outcome domains including different: healthcare systems, social cultures and differences in disease manifestations (Boers et al., 2015).

A recent review has highlighted significant variation in the number of international stakeholders from different countries involved in COS development: ranging between 1-46; median of four countries per COS (Gargon et al., 2014). OMERACT conferences and other developed COS are well represented from North America and Europe, with lower levels of representation from Australasia, South America, Africa and Asia (Boers et al., 2015, Gargon et al., 2014).

2.2.2.4. Stakeholder contribution in the COSCA study

COSCA Research team (Research partners)

A multi-disciplinary research team, representing all relevant stakeholders was established. The group oversaw the design and management the study and consisted of three smaller sub-groups:

- 1) Core team: Laura Whitehead (PhD student), Dr Kirstie Haywood (supervisor) and Professor Gavin Perkins (supervisor).
- 2) An international, multi-perspective steering group consisting of clinical academics: Jonathan Benger, Maaert Castren, Judith Finn, Kenneth Spearpoint, Jerry Nolan, Steve Brett and Vinay Nadkarni.
- 3) Patient research partners: members of the Clinical Research Ambassador Group (CRAG).

LW led the study, generating key ideas for the COSCA study, informed by the current literature and consultation with the core team, steering group and

patient partners. LW was responsible for study design, data collection, analysis and reporting.

The steering group represented four nationalities (UK, Australia, Finland and America) and included expertise in: large cardiac arrest effectiveness trials, pre-hospital care, qualitative research and the measurement of health outcomes. Several members also had affiliations to resuscitation bodies and councils including: International Liaison Committee on Resuscitation (ILCOR), European Resuscitation Council (ERC), the Australian Resuscitation Council (AusRoC), American Heart Association (AHA) and Resuscitation Council UK. Engagement with the steering group took place remotely via webinars and email correspondence.

Patient partners were sought from an established PPI group - the Clinical Research Ambassador Group (CRAG), hosted by Heartland Hospital Birmingham (Heart of England NHS Foundation Trust). CRAG was established in 2012 to aid patient and public involvement across a wide range of research studies. All patient partners had received introductory training to research including Good Clinical Practice. The group consisted of 20 active members aged 40-75 years with experiences across a range of health care areas (Skilton et al., 2016). A subset of patient partners had experience in the field of cardiovascular disease views were sought separately from the full CRAG group on occasions. This subset included a survivor of in-hospital cardiac arrest, two patients that had heart attacks and their partners' and a member with family history of heart disease.

Consultation with patient partners occurred in a variety of settings. This included face to face meetings with the subset of partners with a specific interest in cardiovascular disease. Additionally, study details were discussed with the wider CRAG group at coffee meetings discussed a number of different studies. Email correspondence was used for consultation between planned CRAG meetings. Patient and public involvement will be detailed in relevant chapters.

Research participants

The COSCA study sought to capture the views of key, international stakeholders in cardiac arrest research. This included: healthcare professionals involved in the management of cardiac arrest patients, researchers conducting research on cardiac arrest patients, methodologists, survivors of cardiac arrest and their partners. Healthcare professionals and researchers from a range of patient treatment and research focusses across the patient journey were considered, from the point of cardiac arrest across their time receiving treatment by emergency services and in hospital, extending into post-rehabilitation care. Healthcare professionals from a range of clinical backgrounds were sought to participate including: physicians, nurses and allied health professionals (including paramedics). Views of cardiac arrest survivors that had been discharge home for at least three months and their partners were sought.

2.2.3. Defining and exploring outcomes: which outcome domains should be considered for inclusion in the COS?

The first stage of COS development required identification of a pool of potential outcome domains for inclusion in the core domain set. Identification of potential outcome domains may be identified by a range of sources including: what is currently reported in the literature and considering the views of individual stakeholders. COS without rigorous methods to consider identification of potential outcomes raise challenges and may not include all the outcome domains important to multiple stakeholders. Different sources for the identification of important outcome domains considered for CDS are discussed next.

2.2.3.1. Reviews of outcome reporting

Reviews of outcome reporting across published trials can highlight the degree of heterogeneity, further supporting the need for the development of a COS in a particular health area. A review of outcome domains currently reported provides an indication of outcomes reported across a range of trials across a particular healthcare area. For example in 51 studies in patients with acute stroke: 34 reported death; 14 reported impairment; 11 reported activity; 1 reported quality of life and a further 8 studies reported outcomes categorised as miscellaneous (Duncan et al., 2000). Another review, exploring outcomes reported in studies of inhaled corticosteroids for treating childhood asthma, reported that from 159 studies: 157 reported disease activity, 25 reported functional status 135 reported adverse events, 21

reported quality of life and 17 reported resource utilisation (Sinha et al., 2009). When exploring how recovery from low back pain is reported, 86 different measures were reported across 82 studies and 59 of the measures identified were not reported in more than one study (Kamper et al., 2011).

Reviews of outcome reporting in published trials is time consuming. A recently suggested approach to identifying outcome domains is the analysis of trial registries listing the outcomes reported in ongoing trials (Fabricius et al., 2015). Trial registry extraction has the advantage of identifying outcomes from ongoing and unpublished research. Outcome domains may be more easily identified from trial registry and may highlight discrepancies where outcome reporting bias is present (Dwan et al., 2008). It has been reported that systematic reviews and literature reviews of current outcome reporting have been completed in a large number (n=84, 37%) (Gargon et al., 2014, Gorst et al., 2016) of approaches considering which outcomes should be measured in trials.

Reviews have also highlighted challenges associated with a lack of transparent reporting of methods of assessment and the use of heterogeneous terminology. For example, reviews of outcome reporting in oesophageal cancer (Blencowe et al., 2012) and colorectal cancer (Whistance et al., 2013) reported 10 different definitions of post-operative mortality and 84 different assessments of mortality respectively. In a review of outcome reporting in reconstructive breast surgery, across 134 studies

950 complications were reported and less than 20% of these were defined (Potter et al., 2011).

2.2.3.2. Qualitative research to identify important outcomes

COS development should consider the importance of outcome domains from a range of stakeholder views. Qualitative research may aid the understanding of the importance of outcome domains. This is particularly of use for stakeholders such as patients and the public that are rarely involved in the selection of outcome domains assessed in current ongoing and completed trials. The degree of stakeholder involvement may differ in health research areas with varying levels of recommended stakeholder involvement/patient and public involvement adopted in research communities (Keeley et al., 2016, Chalmers and Glasziou, 2009). Qualitative research gives voice to individuals and rich insights into experience and views which are not attainable from quantitative methods such as surveys (Pope and Mays, 1995).

Different methods of data collection, data analysis and their application within COS development will be discussed:

Data collection

Both interviews and focus groups were considered as potential methods of data collection to identify outcome domains of importance to stakeholders. Considerations informing selection of qualitative approaches for the COSCA study included: the nature of data collection, the subject matter and the study

population (Keeley et al., 2015, Ritchie et al., 2013). To better understand outcomes that are important to stakeholders in COS development qualitative data may be collected in interviews or focus groups which will be described.

Interviews

Qualitative interviews can provide an in depth understanding of the individuals' experience, allowing participants to control the discussion and ensure that important points are covered (Holloway and Wheeler, 2013). Interviews offer the benefits of location and time flexibility causing minimum inconvenience to participants. This ensures that the participant is able to talk in detail for as long as they wish about a topic which may not be possible in a larger group setting. Interview settings can promote ease for the participant and increase openness in a comfortable environment (Dicicco-Bloom and Crabtree, 2006). In the interview setting any upset can be resolved with a minimisation of embarrassment.

Interviews with patients

Several studies describe the use of qualitative interviews to inform COS development with qualitative interviews.

Interviews were conducted with 23 patients with rheumatoid arthritis (RA) to inform the development of a patient core set, this is a group of the most important patient reported outcomes to complement the current COS developed by professionals only (Sanderson et al., 2010b). Participants were purposively sampled to include only patients treated with pharmacological

medication(s). A grounded theory approach to analysis supported identification of 63 different outcomes, which were grouped into eleven categories and further into four broader categories: RA under control (symptoms less, RA stable, medication effects); doing things (doing things able to plan); emotional health (positive feelings, holistic identity, positive mental changes, better life) and coping with illness (coping with RA, coping with health system). Subsequently findings were rated on their importance in a nominal group technique with patient participants, results supported and extended the professional core outcomes (Sanderson et al., 2010a).

During development of a COS for cleft palate with otitis media effusion, 43 parents of 37 affected children (aged 0-11 years) and 22 affected children (aged 6-11 years) were interviewed separately (Tierney et al., 2015).

Interviews with children were assisted using tablet computers. The majority of interviews were conducted at participants' homes with the remainder conducted at the clinic at the parents' request. The interview topic guide did not focus on outcomes with the view that participants would talk about important outcomes on their own accord (Harman et al., 2015). Key themes related to: emotions, educational experiences and social interactions.

Interviews themes were cross referenced with results of a literature review and suggested outcome domains included in a modified Delphi survey. No additional outcomes from the qualitative interviews were identified for consideration as part of CDS, but results supported the selection of outcomes currently reported infrequently in trials (Harman et al., 2015, Tierney et al., 2015). For example from 49 studies included in the literature

review, two studies reported outcome domains related to psychosocial development and six studies reported outcome domains related to behaviour, these infrequently reported outcome domains were identified as important to interview participants (Keeley et al., 2016). Psychosocial development was included in the final ten item core domain set (Harman et al., 2015).

To inform COS development for chronic post-surgical pain after total knee replacement, fifty patient were interviewed (Wylde et al., 2014). Qualitative methods and findings are reported poorly and are referenced under a case analysis study with no detail of the qualitative aspect (Howells et al., 2014). However, the COS publication indicates two new pain features were introduced resulting from interview finding these were: knee pain improvement since the operation and whether knee pain is controllable (Wylde et al., 2014). The final eight outcome domain COS included several descriptors of pain including pain intensity, the use of pain medication and improvement and satisfaction with pain relief which overlaps with the newly identified outcome domains from interviews with patients.

Interviews at 4 weeks and 4 months postoperatively were conducted with 19 hip fracture patients, 14 carers and 8 patient/carer dyads to inform development of a core outcome set for hip fracture (Haywood et al., 2014a). Outcomes judged as important to patients and their partners included: mobility, the ability to complete valued day to day activities, personal care, pain, mental wellbeing and leg shortening (Griffiths et al., 2015). Of these,

pain and activities of daily were included in the five-domain COS, along with HRQoL which may capture aspects of mental wellbeing.

Recent publications have reported qualitative interviews as part of core outcome set development, however these findings are limited and are presented as findings from other qualitative studies (Potter et al., 2015a, Wyldes et al., 2014). The publication of the COS or qualitative interviews fail to transparently report the benefits or disadvantages of conducting qualitative interviews to inform outcomes to consider as part of a core outcome set.

Focus groups

Focus groups provide the benefit of bringing together the views of large numbers of people, at low cost and within a short period of time (Stewart and Shamdasani, 2014). Another advantage is the production of additive data representing a range of views and development of ideas that may not occur in individual interviews. Focus groups normally involve a group of 6-12 participants and are sampled to incorporate a range of participant characteristics (Bowling, 2014). However, this may result in generalised findings rather than a deeper understanding on an individual level.

A limitation of focus groups is that there is the potential for more vocal participants to dominate and influence the group discussion (Stewart and Shamdasani, 2014). Focus groups are constrained by time as a result, outcome domains important to more vocal participants being the focus of discussion missing a range of outcome domains important to the whole

group. Participants may leave the focus group feeling like they have not been able to discuss everything that is important to them as an individual.

Talking about surviving a cardiac arrest or a partner surviving a cardiac arrest is a personal and sensitive topic with potential to cause distress. Due to the sensitivity of the subject many potential participants may not feel comfortable discussing their personal experience in a focus group setting amongst a group of people they are unfamiliar with and there is limited confidentiality (Bowling, 2014). However, authors have described how some sensitive topics, for example sexual health, focus groups can give participants confidence and they may be more open than in a one to one interview (Holloway and Wheeler, 2013).

The time constraints of focus groups also rely on a number of participants being available to attend at a specific time (Stewart and Shamdasani, 2014). The ability of participant to attend depends on the characteristics of the participant group. For example, after a patient has had a cardiac arrest they are unable to drive until 6 months after, meaning that travelling to hospital to participate in a group discussion may be a burden. Additionally, patients may experience new physical symptoms that may make the attendance of focus groups at set times inappropriate.

Focus groups with patients

An early illustration of focus groups supporting the exploration of the outcomes that really matter to patients was with rheumatoid arthritis (RA) patients identified from UK-rheumatology clinics (Carr et al., 2003). Five focus groups with up to 6-9 patients per group (total 39), reflecting a broad spectrum of RA experiences were conducted by research nurses.

Participants were invited to consider the important outcomes from treatment, what makes them satisfied or dissatisfied with a treatment and how they decide whether a treatment is working. Participants highlighted fatigue, sense of well-being and disturbed sleep as the most important aspects of life affected by their RA. Three of these concepts – fatigue, well-being and sleep, were not included in the clinician-derived COS for RA (Boers et al., 1994).

This research along with another qualitative study (Hewlett, 2003) and conference discussions (Kirwan et al., 2003), supported the introduction of fatigue in the established core outcome set for rheumatoid arthritis (Kirwan et al., 2007).

In COS development for Connective Tissue Disease related Interstitial Lung Disease(CTD-ILD) and Idiopathic Pulmonary Fibrosis (IPF) considered the patient's perspective of important outcome domains in focus groups. 45 patients including a range of disease states participated in 6 focus groups of 8-12 participants (Saketkoo et al., 2014b). Focus group discussions highlighted the centrality of 'cough' to patient status, having a wider impact on physical functioning, sleep and social aspects of health related quality of life. Cough was an outcome domain dismissed in a modified Delphi survey

with healthcare professionals. Additionally, patients discussed what dyspnoea meant to them. Frequently terms such as 'winded' and 'losing breath' were used but patient described shortness of breath as more appropriate. Patients explained how this influenced their daily activities such as completing tasks and reading to children (Saketkoo et al., 2014a). Dyspnoea and cough were included in the 6 outcome domain COS but highlighted a need for further validation and development of appropriate measurement tools (Saketkoo et al., 2014a).

Focus groups with healthcare professionals and researchers

In the development of a COS for chronic surgical pain after total knee replacement, four focus groups were conducted with 18 clinicians to explore important outcome domains (Wylde et al., 2014) (MacKichan et al., 2014). Limited information was detailed about the methods and results of this qualitative exploration, which limits the interpretation and transferability of this study. However, focus groups resulted in the addition of three outcome domains to consider for COS inclusion, these were: knee pain interference with everyday activities, knee pain interference with social, family or leisure activities and dose of medication to relieve pain (Wylde et al., 2014). Pain interference with everyday activities was included in the final 8 outcome domain COS.

Data analysis

Approaches to qualitative analysis include: grounded theory; ethnography; thematic analysis; framework analysis; discourse analysis; phenomenology and interpretative phenomenological analysis (IPA). Key characteristics of potential approaches are detailed in table 2.1. Each approach was considered for application in the COSCA study, informed by analysis characteristics and application in COS.

Grounded theory has been applied in studies of COS for development for breast reconstruction (Potter et al., 2015b), ongoing pain after knee replacement (Howells et al., 2014) and rheumatoid arthritis (Sanderson et al., 2010a). Grounded theory was not considered appropriate for the COSCA study because the COSCA study seeks to identify important outcomes to patients through understanding their lived experience. Generating theory is a key aspect of grounded theory and the COSCA study did not seek to generate a theory surrounding why these outcomes are important.

No examples of ethnographic studies or discourse analysis were identified in the aiding development of core outcome sets. Ethnography aims to understand the social interactions of group members, exploring the nature of phenomenon's; an observation approach would be problematic logistically and difficult to aid the understanding of which outcomes are important to a population (Reeves et al., 2008). Discourse analysis focuses on the understanding of linguistics and was judged to be inappropriate for identifying important outcome domains (Jørgensen and Phillips, 2002).

Thematic analysis has been used in the development of COS for hip fracture (Griffiths et al., 2015) and ongoing pain after knee replacement (MacKichan et al., 2014). Thematic analysis is an appropriate method to identify themes and outcome domains that are important to patients. However, thematic analysis may be viewed as the coding process of qualitative analysis and can be descriptive without application to an existing theoretical framework (Braun and Clarke, 2006).

Table 2.1: Approaches to qualitative data analysis

Analysis approach	Key characteristics
Grounded theory (GT)	Grounded theory generates theory from data (Glaser and Strauss, 2009), exploring the social processes of phenomena occurring in the context of a particular environment (Starks and Trinidad, 2007). An iterative approach is taken with constant comparison between cases and analysis informing the conduct of subsequent data collection. Sampling is purposive to capture a range of experiences and sample size informed by data saturation (Starks and Trinidad, 2007).
Ethnography	Ethnographic studies the social interactions and behaviours of groups (Reeves et al., 2008).
Thematic analysis	Thematic analysis identifies, analyses and reports themes or patterns within data (Braun and Clarke, 2006). Some authors consider thematic analysis a coding process as part of data analysis, whereas others argue it should be treat as a method.
Framework analysis	Framework analysis draws conclusions from a theme and case based analysis (Ritchie and Spencer, 2002). Aiding analysis a chart is produced with columns representing cases different and rows representing different themes. Framework analysis is conducted by a team of qualitative researchers which can results in a transparent and rigorous analysis (Dixon-Woods, 2011).
Discourse analysis	Discourse analysis seeks to understand how people use language to describe their understanding of an experience (Jørgensen and Phillips, 2002).
Phenomenology	Phenomenology is the study of the lived experience of a phenomena (Starks and Trinidad, 2007).
Interpretative Phenomenological Analysis (IPA)	IPA is dedicated to understanding an individuals' lived experience of a phenomena. IPA has theoretical underpinnings in: phenomenology, hermeneutics and idiography. Sample sizes are smaller than other approaches focussing on the individuals' experience (Smith et al., 2009).

Framework analysis was applied in development of a COS in cleft lip and palate (Tierney et al., 2015). Similarly to thematic analysis, framework analysis is considered a methods of analysis and not underpinned by theory (Ward et al., 2013). Framework analysis is conducted by a team increasing rigour and transparency in analysis (Dixon-Woods, 2011). Analysis is supported by the comparison of themes and cases which could help aid identification of important outcomes in COS development (Ritchie and Spencer, 2002).

Phenomenology is the study of phenomenon (or an experience), aiming to either describe the phenomenon or develop and understanding of the phenomenon through interpretation (Holloway and Wheeler, 2013). More recently the development of Interpretative Phenomenological Analysis (IPA) has occurred, dedicating understanding to idiographic experiences and reflecting on the diversity of experience (Biggerstaff, 2012). Interpretative phenomenological analysis (IPA) was applied in rheumatoid arthritis focus groups informing the update of a COS for RA (Carr et al., 2003). This approach has strengths in COS with a commitment to understanding an individuals lived experience.

2.2.3.3. Defining and exploring outcome domains in the COSCA study

Systematic review of current outcome reporting

To answer the first research question of which outcomes are currently reported in cardiac arrest randomised control trials, a systematic review was selected. The ICF framework classification was selected as the most appropriate to classify reported outcomes, at this time point the OMERACT 2.0 filter had not been published. This systematic review is described in chapter 3.

Qualitative exploration of outcome domains with cardiac arrest survivors and their partners

A number of different methods were considered to capture the views of both healthcare professionals and patients that have survived a cardiac arrest to support the information obtained from the systematic review.

Focus groups with healthcare professionals were considered to explore the views of this healthcare professionals and researchers further to identify any potential missing outcomes important to this stakeholder group. It was concluded that due to clinical trials being conducted and designed from the perspective of clinical researchers, it was unlikely that focus groups would yield sufficient additional outcomes of interest to this stakeholder group to justify this as additional method. To ensure no important outcome domains were missed from the perspective of this stakeholder group, at the start of

consensus development there would be an opportunity to list any missing outcomes.

Evidence suggest that outcomes important to cardiac arrest survivors are currently reflected in cardiac arrest randomised control trials, with outcomes selected historically from the researchers/healthcare professionals perspective (Sawyer and Kurz, 2015, Haywood et al., 2014b, Trzeciak et al., 2009, Whitehead et al., 2015). Qualitative research to understanding the outcomes important to survivors in this area is limited. It was concluded that semi-structured interviews were required to be conducted with cardiac arrest survivors and their partners to answer research question 1.2: which outcomes really matter to patients who have survived a cardiac arrest.

The value of partner/carer qualitative exploration was considered important as cardiac arrest survivors may experience some cognitive impairments and memory gaps of the time periods immediately before and after their arrest. These factors could impact patient recall and understanding. Experience of attending home visits for a study of cardiac arrest survivors (Perkins et al., 2010), highlighted the benefits of involving patients' partners in the qualitative exploration to gain a fuller understanding of the patients' lived experience were considered. In addition to this partners/carers may have different views on perceived changes in health status as reported when assessing proxy completion in other health conditions (Dorman et al., 1997, Haywood et al., 2014b).

Interviews were selected due the appropriateness of approach for cardiac arrest survivors as research participants. Interviews allow patients to discuss their experience of surviving a cardiac arrest retaining sensitivity and at minimum inconvenience. Interviews allow a deep understanding of each participants' individual recovery which may indicate variability between individual experiences. It was also anticipated focus groups may be poorly attended and patients would favour interviews, which could be organised at their convenience and at setting of their choice.

From approaches to qualitative analysis considered it was concluded Interpretative Phenomenological Analysis was judged to be the most appropriate analysis to achieve the aims of the COSCA study. IPA was selected due to a commitment to understanding the individual lived experience.

2.2.4. Achieving consensus: what does consensus mean and how can it be achieved?

2.2.4.1. Why consensus methods are needed

Consensus development is important for making recommendations when there is a limited or conflicting evidence base from which to draw conclusions (Jones and Hunter, 1995). Consensus development serves the role of informing guidelines and not the generation of new information (Murphy et al., 1998). Consensus development can be either structured or unstructured.

Unstructured consensus methods such as round table discussions have a number of limitations including the domination of individuals, the pressure on participants to agree, extreme views receiving greater support than they would on an individual level and complex issues may remain unsolved (Black, 2007). Structured methods such as nominal group techniques and Delphi surveys have increased methodological rigour, attempting to control a number of influential factors including dominating individuals, reducing potential biases and promoting transparent and reproducible methods.

Structured formal consensus methods make a number of assumptions about the decision making process (Murphy et al., 1998). Consensus methods rely on a safety in numbers, assuming that the more people involved in the consensus process the more likely that this is going to be correct view. It is assumed structured processes meet scientific requirements and the group selected will take a degree of ownership for the meeting outcome.

Consensus methods have the advantage of filtering out idiosyncrasies and that a view informed by consensus of a group carries more weight than the view of an individual. Features of consensus methods include: evidence to guide discussion and opinion, privacy of views, the opportunity to change views and an explicit and transparent reporting of group discussion (Black, 2007).

Consensus development is based on the decisions of individuals and group contributions. There are a number of psychological processes that can impact on decision making including: attention and memory; problem solving,

reasoning, thinking and decision making; social cognition; persuasion and attitude changes and behaviour within groups (Murphy et al., 1998).

Individual bias either cognitive or motivational can influence decision making (Murphy et al., 1998). Cognitive bias considers the need to have a coherent and logical approach and motivational biases are driven by individual and group needs.

The decision making process involved in voting for core outcome domains for CDS inclusion has not been previously explored. Participants in COS development consensus methods are required to determine the importance of outcome domains for COS inclusion, there a number of considerations and factors that may influence participants' decisions. These may include the views of others participants including differing stakeholder groups via remote consensus method feedback in surveys or through interactive face to face discussions. In addition to this individual views surrounding outcome reporting and measurement including: cost, feasibility and available measurement tools may influence voting in COS development.

2.2.4.2. Formal consensus methods

Once potential outcome domains have been identified, consensus development is required to recommend which outcome domains are the most important and should be reported as part of a CDS. A recent review of 198 studies considering methods to select outcomes reported in studies, indicated 54% were defined by semi-structured discussion groups and 12% through unstructured groups discussions (Gargon et al., 2014). This review

illustrated specific methods adopted by COS developers, including: modified Delphi surveys (15%), consensus development conferences (10%), surveys (9%) and modified nominal group techniques (NGT) (8%). Single or multiple consensus methods may be applied, it has been suggested that a survey method in combination with a face to face meeting can be beneficial, combining the benefits of each method increasing reliability, consensus and understanding (Hutchings et al., 2006, Raine et al., 2005). Both survey and face to face formal consensus development methods will be summarised followed by a description of application in COS development and participant considerations.

Survey methods: *Modified Delphi survey*

Traditionally, the classical Delphi (Dalkey and Helmer, 1963) begins with a qualitative question to generate information and ideas before seeking to develop consensus. This approach was first reported in technological forecasting in the Cold War to bring achieving convergence of expert views (Dalkey and Helmer, 1963, Hsu and Sandford, 2007b). A Delphi survey is characterised by multiple rounds of survey with feedback between rounds and the opportunity to alter responses (Hsu and Sandford, 2007b).

Modifications of the original Delphi survey are frequently used in health research beginning with consensus development of items informed from various sources (Hasson and Keeney, 2011). Data sources that may inform a Delphi survey include: literature reviews, interviews, focus groups and panel meetings.

An advantage of the Delphi survey is that through advances in technology surveys can be applied electronically with a number of associated benefits. Electronic survey application allows the collection views of large number of experts from diverse geographical populations are able to contribute at a low cost, over shorter time commitments and at participant conveniences, which alternative consensus development approaches may not allow (Hsu and Sandford, 2007b). However, a major limitation of online surveys is their representation as this may restrict the sample to limited age range and economic background. Due to the ability to involve more participants to Delphi surveys have a higher reliability than nominal group techniques (Black, 2007). However Delphi surveys produce a lesser degree of consensus than NGTs, this is because NGT involves shared discussion and the reasoning of scores in face to face interactions (Hutchings et al., 2006).

A Delphi survey is controlled and anonymous, meaning participants can respond honestly and consensus is not driven by dominant individuals that may influence results in other consensus development approaches such as face to face consensus meetings, panel meetings and round table discussions (Hasson et al., 2000, Dalkey and Helmer, 1963). Delphi surveys, and modifications of the approach, have been widely applied in various healthcare arenas. For example, to capture the views of international experts in development of: standardised measurement taxonomy, terminology and definitions of PROMS (Mokkink et al., 2010), clinical trial protocol content checklist (Tetzlaff et al., 2012) and reporting checklist for patient and public

involvement (Staniszewska, 2014). The process has also been used to support : Consensus development of definitions of neurodisability (Morris et al., 2013), to set research priorities in intensive care (Reay et al., 2014) and informing registries for uniform data reporting in major trauma (Ringdal et al., 2008), physician staffed pre-hospital services (Krüger et al., 2011), pre-hospital advance airway management (Sollid et al., 2009) and cardiac arrest (Perkins et al., 2014). More recently, the COMET group conducted a modified Delphi survey with published, international developers of COS to establish international consensus on Core Outcome Set-STAndards for Reporting (CO-STAR) (Kirkham et al., 2015).

Modified Delphi surveys in COS development

Reviews have highlighted a wide application of modified Delphi surveys in the consideration of outcome domains in trials on at least 38 occasions (Gargon et al., 2015b, Gorst et al., 2016), including consensus development in COS in the field of : eczema (Schmitt et al., 2011); fibromyalgia (Mease et al., 2008); acute diarrhoea (Karas et al., 2014) and psoriatic arthritis(Taylor, 2005) to name a few.

As described the modified Delphi survey brings a number advantages with the option of online application including the potential participation from a large and diverse groups at a low cost. For example for COS development for breast cancer (Potter et al., 2015a), maternity care (*Devane et al., 2007*) , CTD-ILD and ILD (Saketkoo et al., 2014b) and flare in RA (Bartlett et al., 2012) more than 200 participants completed the first round of the modified

Delphi survey. Further to this, COS development in RA flare (Bartlett et al., 2012), maternity care (Devane et al., 2007), vitiligo (Eleftheriadou et al., 2015) and disease activity and damage assessment in JSLE and JDM (Ruperto et al., 2003) have had participants from more than 20 countries completing modified Delphi surveys.

Face to face methods

Nominal group technique

The Nominal Group Technique (NGT) was first used by Delbecq and Van de Ven in 1971 in a committee decision making process (Delbecq and Van de Ven, 1971). The Nominal group technique (NGT) is widely used in consensus development. A typical NGT follows 5 key steps: 1) introduction and explanation of the concept, 2) the silent generation of individual ideas, 3) sharing ideas, 4) group discussions and 5) voting and ranking exercises (Potter et al., 2004). Many modified versions of the NGT are applied across healthcare. An established modification of the NGT is the RAND method. The RAND method involves a pre-meeting questionnaire (Fitch et al., 2001). NGT often have a range of 8-12 participants (Black, 2007), too few participants can limit the reliability of findings and too many participants can make activities difficult to manage (Richardson, 1972).

Strengths of the nominal group technique include a formalised process where individuals are able to respond, discuss and consider different options as well as voting for them. With remote methods such as Delphi surveys there is not the opportunity to discuss the reasons for and against a choice

which in a face to face meeting will impact voting. This results in higher levels of consensus and further understanding of conclusions (Hutchings et al., 2006).

Nominal group technique and Core outcome sets

There have been at least 15 reported of the nominal group technique applied in a review of methods to select outcomes in trials (Gorst et al., 2016, Gargon et al., 2014), although not stated in the review many of these are modifications of the traditional NGT. Two examples of transparently reported nominal group techniques to develop consensus on outcome domains to include as part of a COS are described.

In the field of Juvenile Dermatomyositis (JDM) and Juvenile Systemic Lupus Erythematosus (JSLE) 40 paediatric rheumatologists from 34 countries attended a four day meeting (2 days allocated for each disease area) seeking define core sets (Ruperto et al., 2003). Prior to the meeting an information synthesis was circulated summarising a modified Delphi survey informing the meeting content. At the meeting participants were randomly allocated into three groups completing five NGT exercises in separate rooms, each group was moderated by a moderator with experience in NGT. Exercises 1 and 2 focussed on the classification of variables and their definitions. Exercise 3 asked participants to select and rank outcomes that should be included in the core sets. Exercise 4 invited participants to select variable to measure outcomes and exercise concluded with participants defining inclusion and exclusion criteria for a data collection study in the

validation of the preliminary core set. Scores were obtained within groups and totalled, requiring a 80% level of consensus for inclusion (Ruperto et al., 2003).

In development of a CDS and COMS for hip fracture, Haywood and colleagues applied the RAND modification of the NGT (Haywood et al., 2014a). A pre-meeting survey was conducted asking participants to: rate the importance of outcome domains for inclusion in a COS on a 9-point Grade scale; rate the feasibility of outcome measures on a 9-point Grade scale; finally, the suitability of outcome measures for clinical trials of hip fracture was sought (yes or no response). The face to face meeting was chaired by an independent chair and began with the presentation of an evidence synthesis and pre-meeting votes (individuals received a copy of their scores), before a semi-structured discussion and smaller group discussions. The meeting was attended by 15 participants including: healthcare professionals, researchers, policy makers, funding bodies and 3 lay members who were carers for partners with hip fracture. Interactive voting sought 'yes' or 'no' votes for COS inclusion for outcome domains and measures. A high level of agreement (70%) was required to achieve consensus. The final vote resulted in a five outcome domain COS.

OMERACT hold face to face consensus methods alongside conference meetings, although these are described as a loose variant on the nominal group technique (Boers et al., 2015), describing individual generation of ideas with structured discussion and voting taking place.

Consensus meetings

In addition to NGT there are other structured face to face meetings that seek to reach consensus. The review of methods to select outcomes reports semi-structured and structure consensus development in: consensus development conferences, workshops, meetings and round table discussions (Gargon et al., 2014). However, there is a lack of clarity in the different qualities of these methods with terminology often used interchangeably. Face to face methods often lack transparency and detail of methods conducted, providing limited guidance for researchers.

Consensus development conferences are held with a selected panel (approximately 10 people) often over a number of days alongside a conference (Murphy et al., 1998). Interest groups and experts will present findings to help participants to inform their decision with the opportunity to ask questions. In the consensus development conferences there is no implicit method for the aggregation of views, no formalised feedback and discussions do not occur in private, these characteristics limit the methodological rigour in comparison of other consensus development methods and do not account for impact of dominant individuals (Halcomb et al., 2008). Consensus development conferences have previously been applied for the formulation of National Institute of Health (USA) guidelines (Black et al., 1999).

Consensus meetings in COS development

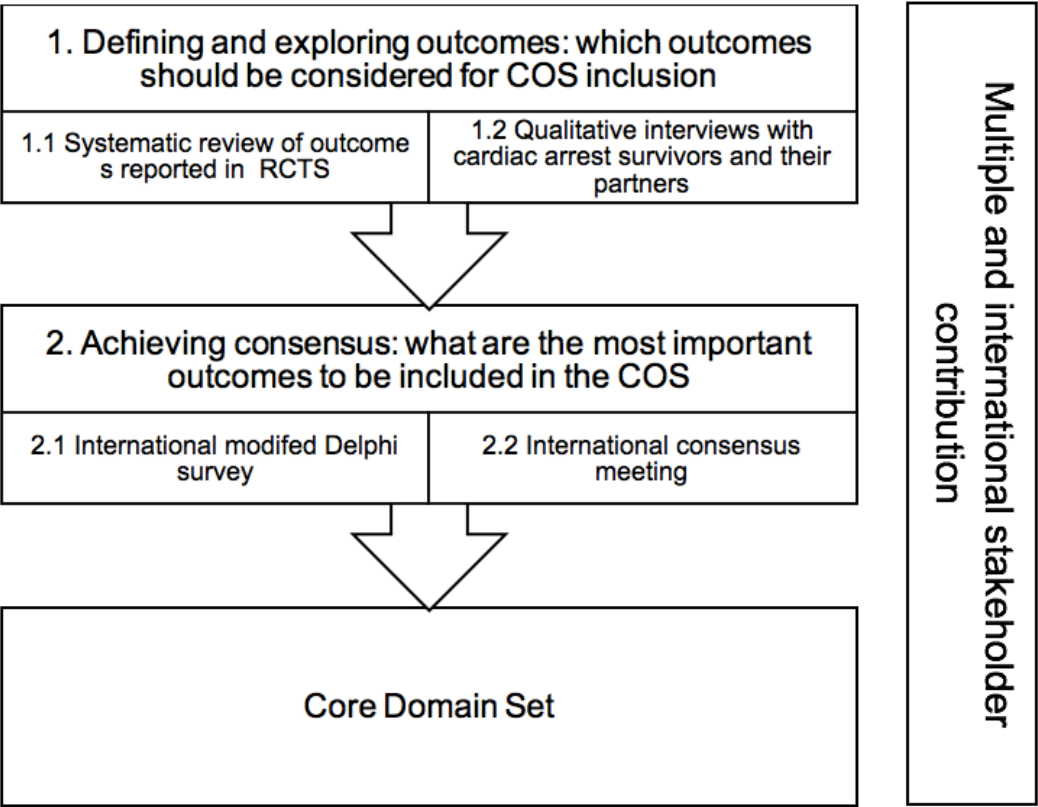
Despite 10% of studies described including consensus conferences in the review of studies exploring choosing outcomes to be assessed, no transparent reports of consensus conference in the development of core outcome sets were identified to inform the COSCA methods. COS developers have reported 'consensus meetings' (Harman et al., 2015, Potter et al., 2015a) describing meetings held by an independent facilitator including summaries of work to date, discussions and anonymous voting.

2.2.4.3. Achieving consensus in the COSCA study

In order to engage with a large international audience, capable of providing multiple stakeholder perspectives on the importance of outcomes for reporting CA effectiveness trials, a two stage consensus development process was adopted. This approach provided the benefits of both electronic survey approaches and face to face discussions.

1) First, an international modified Delphi e-survey with multiple stakeholders and 2) An international consensus meeting. The face-to face consensus meeting would also facilitate initial discussions of how to measure the shortlisted outcome domains reaching consensus for inclusion in a CDS. Further details of the selected methods are described in chapter 5 and 6. The key stages and proposed methods for the COSCA study are summarised in Figure 2.2

Figure 2.2: Overview of the selected methods for the COSCA study



Chapter 3: A systematic review of outcomes reported across cardiac arrest randomised controlled trials

The findings of this study have been published in the journal Resuscitation:
Whitehead, L., Perkins, G. D., Clarey, A. and Haywood, K. L. (2015) 'A systematic review of the outcomes reported in cardiac arrest clinical trials: The need for a core outcome set', Resuscitation, 88C, pp. 150-157.

3.1. Introduction

In this chapter the first steps towards defining and exploring outcome domains to include in a core outcome set, a review of outcome reporting across cardiac arrest randomised control trials will be described. The questions of 'what' and 'how' outcome domains are currently reported across cardiac arrest RCTs are reported will be explored, reaffirming the homogenous nature of outcome reporting in this field and a need for a core outcome set. The findings of the review will also provide a preliminary list of outcome domains to consider for inclusion as part of a core outcome set.

Section 3.2 will describe the methods applied to identify relevant studies and the process of data extraction. Section 3.3 will describe the nature of outcomes reported, their frequency, time point of assessment and the reproducibility of assessment. Section 3.4 will summarise the key findings of the review and the findings in the context of the cardiac arrest literature.

Aim:

The aim of this review was to explore outcome reporting in cardiac arrest randomised controlled trials, identifying trends and heterogeneity. This review sought to produce a preliminary list of outcomes to be considered for COS inclusion, primarily representing the views of healthcare professionals and researchers from the field of cardiac arrest care.

3.2. Methods

3.2.1. Search strategy and study selection

Search strategy

A search strategy was developed with the assistance of an experienced librarian (SJ), to identify all randomised controlled trials enrolling cardiac arrest patients irrespective of location, published between 2002 and 2012. A wide range of search terms were included to identify all trials of interest; search terms are listed in Appendix 3.1. The search strategy was applied (January 2013) to four databases: Medline Ovid, EMBASE Ovid, CINAHL and the Cochrane library.

Inclusion criteria for this review were: randomised controlled trials including adult cardiac arrest patients irrespective of location, published between 2002 and 2012. Pilot studies were not excluded from the review unless subsequent full trial studies were identified in the search. Exclusion criteria were: trials that did not include a population that was exclusively cardiac arrest patients (e.g. ST elevation myocardial infarction (STEMI) patients). Trials were also excluded where the patient population included subjects under the age of eighteen or no age lower limits were stated. Only studies with subject over the age of eighteen were included due to the differences in resuscitation care between the adult and paediatric population (Kleinman et al., 2010). The search was limited to studies published in the English language.

Study selection

After the removal of duplicated studies, two reviewers (LW and AC) independently screened titles, abstracts and full texts articles for eligibility. Where disagreement was encountered a third reviewer (KH) provided the deciding vote for inclusion.

3.2.2. Data extraction

Templates were created for data extraction which are featured in Appendix 3.2. The first template reported study specific information: authors, year of publication, title, the location of arrest, the number of study patients, study intervention and whether there was reference to the Utstein templates relevant at the time of publication (Cummins et al., 1991, Jacobs et al., 2004). A second template focussed details of outcomes reporting. For each primary and secondary outcome details of what was assessed (the domain of health), how this was assessed (methods and measurement tools) and when these were assessed. In addition to this the reproducibility of outcomes was reported, this was defined as whether reproduction of measurement was possible with the text and references provided, this was classified as Yes or No.

Three reviewers (LW, KH, GP) completed the data extraction process of a random selection of articles (n=10). Agreement was sought between reviewers and any modifications to extraction was suitably noted. There were no concerns on the interpretation of extraction of outcome domains,

therefore extraction was completed by LW and second opinion was sought from (GP and KH) were outcome reporting was not fully transparent.

3.2.3. Outcome analysis and critical appraisal

Once data were extracted outcome measurement data were categorised into six pre-determined domains. The ICF framework was selected as a useful framework to base domain classification (WHO, 2001, Duncan et al., 2000). In addition to ICF domains of body structure and function, activities and participation, several outcomes reported in cardiac arrest RCTs were suited to the additional domains: survival, health related quality of life and processes of care. Table 3.1 defines and provides examples of each domain. Body structure and function was further categorised into seven sub-domains: circulatory function, cerebral function, other organ function, cardiac rhythm stability, respiratory function, adverse events and fluid regulation. Processes of care were also classified into the following subdomains: cooling device, CPR variables, time to successful treatment or intervention and other.

The range of different outcomes and the frequencies of outcome reporting from each domain were explored. The reproducibility of outcomes in each overall and within domains was investigated. The patterns of outcome reporting over time were explored overall and within domains.

Table 3.1: Conceptual framework for outcome classification (adapted from(Whistance et al., 2013)) ---- published in (Whitehead et al., 2015).

Domain and subdomains	Definition
Survival	Reports of short- and long-term survival/ mortality.
Body structure and function	Body Structure refers to the anatomical structure of organs. Body Function refers to physiological and psychological functioning of body systems.
Circulatory function	Assessments of the circulatory system function. For example, blood pressure, heart rate, oxygen saturation.
Cerebral function	Biochemical measure of cerebral activity or damage. For example, biomarkers, cerebral perfusion and intracranial pressure.
Cardiac rhythm stability	Rhythm analysis or the application of pharmacological agents to control cardiac rhythmicity. For example, episodes of ventricular tachycardia, premature beats.
Respiratory function	Assessments of the respiratory system function. For example, intra-thoracic pressures and end tidal carbon dioxide.
Other organ function	Biochemical markers of system function, such as renal and immune functions.
Adverse events	Reporting of adverse events through time points, serious adverse events and any complications.
Fluid regulation	Assessment of fluid infusion or capillary leakage.
Activities	Ability of an individual to perform an activity or task. Includes assessment of basic and instrumental activities of daily life (e.g. washing, dressing) and walking.
Participation	Ability of an individual to participate in life and related activities, as influenced by their health. Includes work stability, engaging with family life and usual social role.
Health related quality of life	Assessment of the quality of an individuals' life as influenced by their health – how they feel, what they can do, and how they live life. Assessment may emotional well-being, symptoms, physical functioning, level of dependency, and social participation.
Processes of care	Outcomes related to a specific intervention received, also the flow of patients through the healthcare system. Examples approaches to assessment in cardiac arrest include: the efficiency of therapeutic hypothermia, quality of CPR variables and the duration of stay in hospital.

3.3. Results

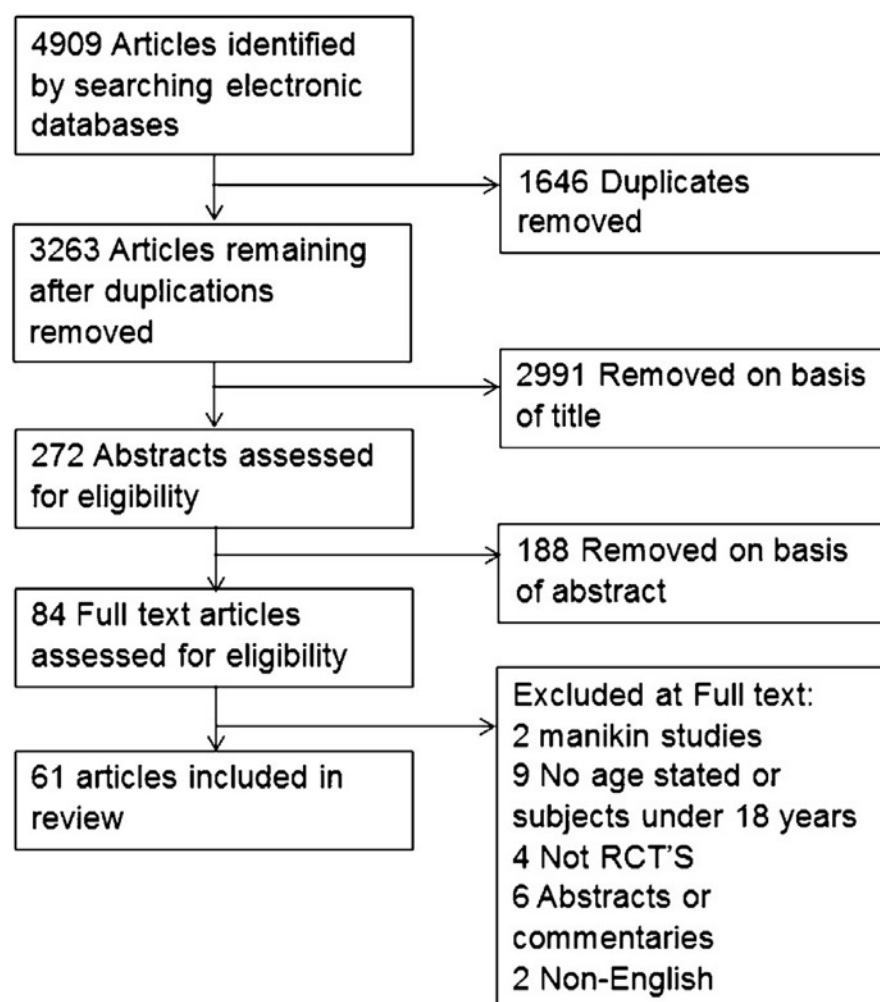
3.3.1. Included studies

After applying the search strategy to the four databases 4909 potential articles were identified (Figure 3.1). Duplications were removed leaving 3263 articles to be screened. 2991 articles were removed based on the title, the remaining 272 abstracts were screened and 84 full text articles were assessed for eligibility.

After full text assessment a further 23 articles were removed leaving 61 randomised controlled trials meeting the inclusion criteria. Reasons for exclusion at full text assessment included: manikin studies; non-RCTs; abstract only or commentary publication; subjects under the age of 18 or no age stated and non-English publications.

The number of participants in each study ranged from 13-9933, with a median of 168 participants (Table 3.2). Studies included an international background including: Europe (35), North America (19), Australia (4) and Asia (3). The relevant Utstein Template and Recommendations for Outcome Reporting were referenced in the majority of studies (n=44: 72%) (Jacobs et al., 2004, Cummins et al., 1991). The majority of studies included the out-of-hospital cardiac arrest population with only 3 out of the 61 studies including patients that had experienced an in-hospital cardiac arrest.

Figure 3.1: Study screening and selection process (Whitehead et al., 2015).



Across the 61 studies there was a range of the study focus but most commonly investigated were: pharmacological applications (33%), therapeutic hypothermia (20%), defibrillation techniques (11.5%) and Impedance Threshold Devices (ITD) (11.5%). In seven (11.5%) of studies it was notably difficult to distinguish between primary and secondary outcome measures.

Table 3.2: Demographic details of studies meeting the inclusion criteria

Study demographics		Number of studies
Number of patients	1-50	10
	51-100	11
	101-500	27
	501-1000	5
	Over 1000	8
Location of arrest of population	In hospital	2 (3%)
	Out of hospital	58 (95%)
	Either	1 (2%)
Type of intervention	Pharmacological	20 (33%)
	Therapeutic hypothermia	12(20%)
	Defibrillation techniques (shock delivery, waveforms, patterns)	7(11.5%)
	Impedance threshold devices	7(11.5%)
	Monitoring and feedback	4(7%)
	Mechanical CPR	3(5%)
	Other	8(13%)
Reference to the Utstein Template (Cummins et al., 1991, Jacobs et al., 2004)	Yes	44 (72%)

3.3.2. Which outcomes are assessed in cardiac arrest randomised controlled trials

Across the 61 studies, a total of 164 individual outcomes were identified, this represents outcomes different in what they measured, how outcome was defined, how they were measured and the time point of measurement. Table 3.3 provides a summary of the number of different types of outcomes reported from each domain and the occurrence of outcomes reported. The domain with the largest number of different outcomes was body structure and function (72), followed by survival (39), processes of care (33) and activities (20). No outcomes were reported from the domains of participation and health related quality of life.

Looking at the reporting of an outcome from each ICF domain in individual studies, survival was the domain with the highest prevalence, being reported in 85.2% (n=52) of studies. Studies displayed a focus on reporting outcomes from the domains activities (52.5%), body structure and function (41.0%) and processes of care (26.2%). Across the 61 studies there was a total frequency of outcomes, considering the frequency of outcomes from each domain reporting was focussed on survival (116= 41.7%), body structure and function (75=27.0%), activities (48= 17.3%) and process of care (39=14.%).

Table 3.3: The classification and patterns of outcome reporting across the 61 studies. 1) The number of individual outcomes reported from each domain. 2) The number of studies reporting outcomes from each study and 3) The frequency of outcomes reported from each outcome domain across studies.

Outcome domains:	1) Number of individual (different) outcomes in each domain:	2) Number RCTs outcome domain was assessed in (Total= 61) (%)	3)Frequency of outcomes reported from this domain*
Survival	39*	52 (85.2%)	116
Body structure / function	72	25 (41.0%)	75
Circulatory function	24	10	
Cerebral function	15	5	
Other organ function	12	3	
Cardiac rhythm stability	7	5	
Respiratory function	6	5	
Adverse events	5	5	
Fluid regulation	3	2	
Activities	20*	32 (52.5%)	48
Participation	0	0	0
Health-related Quality of life (HRQoL)	0	0	0
Process of care	33	16 (26.2%)	39
Total	164		278

Footnote:

*- On six occasions survival and an assessment of activity were measured in conjunction, for example: 'Survival to discharge with Cerebral Performance Category Score'. On these occasions outcomes were classified and counted as an individual activity measurement. These outcomes were included in the count for both survival and activity where exploring the number of RCT's including an outcome from this domain.

3.3.2.1. Survival

Survival was reported in the majority of studies with 52 of the 61 studies including an assessment of survival (85.2%). In 37 (60.7%) and 44 (72.1%) studies survival was reported as primary and secondary outcomes respectively. In some studies, outcomes reported as a measure of activity of level in combination of survival. These outcomes have been included in the count for studies including an outcome from the domain of survival but will be discussed in section 3.3.2.3, describing the reporting from the activity domain.

39 different survival outcomes were identified with variations of definition and time point of measurement (Table 3.4). Table 3.4 details the number of studies reporting each outcome as a primary and secondary outcome and the frequency that each outcome was reproducible. There was a total frequency of 116 survival outcomes reported with a number of studies measuring survival at more than one-time point.

‘Survival to hospital discharge’ was the most frequently assessed survival measure reported in 30 (49.1%) trials. ‘Survival to hospital admission’ was the next most frequently reported survival measure (n=14:23%). Of the 39 different survival measurements, 11 were different measurements of Return of Spontaneous Circulation (ROSC). ROSC measures demonstrated variation in definition, on 12 occasions no detail of definition was reported, further detail of ROSC terminology and definitions are reported in table 3.5.

The most commonly reported ROSC measure was 'ROSC', which was assessed in 10 studies (16.3%).

Survival outcomes were predominantly reported in the short term up to and including at hospital discharge (89.5%). The most common time point survival was assessed after hospital discharge was 'survival at 6 months' (n=3). The time coverage of survival measures ranged from any ROSC up until 3-year survival. The distribution of survival measurements was as follows: 55.4% before discharge, 33.9% at discharge and 10.7% after discharge.

Table 3.4: Survival outcomes: Details of different survival outcomes, frequency of reporting as a primary or secondary outcome and the reproducibility of outcome reporting.

Outcome	Frequency reported as a (1) primary outcome or (2) secondary outcome	Frequency of reproducible outcome reporting
1 year survival	(2) 2	0/2
1hr survival	(2) 1	0/1
1hr survival after hospital admission	(1) 1	1/1
24hr survival	(1) 1, (2) 3	4/4
3 month survival	(1) 1 (2) 1	0/2
3 year survival	(2) 1	0/1
30 day survival	(2) 1	0/1
4hrs after 911 call	(1) 1	1/1
6-month survival	(1) 1	0/1
All cause mortality 30days after ROSC	(1)1	0/1
Any ROSC	(1) 1 (2) 2	3/3
Awakening	(2) 1	1/1
Awakening at 3month	(1) 1	1/1
Days to awakening	(2) 1	1/1
Duration of survival	(2) 1	0/1
Death	(1) 4	3/4
Hospital discharge	(1) 8 (2) 22	30/30
Hospital discharge rate	(2) 1	1/1
Hospital mortality	(2) 1	1/1
ICU admission rate	(2) 1	1/1
In hospital 30 day mortality	(2) 1	1/1
Mortality at 6 months	(2) 2	½
Pre-hospital ROSC	(1) 1 (2) 2	1/3
Pulses on hospital admission	(1)1	1/1
Rate of hospital admission	(2) 2	2/2
Recovery of consciousness	(1) 1 (2) 1	2/2
ROSC	(1) 4 (2) 6	6/10
ROSC >15mins	(1) 1	1/1
ROSC >5mins	(1) 1	1/1
ROSC at emergency department	(2) 3	1/3
ROSC at end of EMS care	(2) 1	1/1
ROSC at scene or at A and E	(1) 1	1/1
ROSC before physician arrival	(2) 1	1/1
ROSC rate	(2) 6	1/6
Sustained ROSC (>2hours)	(1) 1	1/1
To Emergency department	(1) 2	2/2
To hospital admission	(1) 6 (2) 8	4/14
To ICU admission	(1) 2(2) 1	3/3
To ICU discharge	(1) 1 (2)1	2/2

Table 3.5: Definitions of Return of Spontaneous Circulation (ROSC) cited from publications, published in (Whitehead et al., 2015). On 12 occasions no detail of definition was provided.

<p>1. ROSC</p> <ul style="list-style-type: none"> • Admission to hospital with a spontaneous perfusing rhythm (admission formal assignment to bed) • Determined by a palpitation pulse at any time following enrolment with or without detectable blood pressure • ROSC MAP of 50mmHg (no detail of duration) • Defined using the ILCOR definition as any return of a spontaneous pulse, detectable by palpitation of the carotid or femoral artery with no minimum duration • Assumed to have ROSC patients are moved from ER to ICU • ROSC with a palpable pulse • Defined as a palpable pulse for at least 15 seconds
<p>2. ROSC rates</p> <ul style="list-style-type: none"> • ROSC was defined as an organised rhythm and palpable pulse that was sustained for at least 20 minutes
<p>3. Prehospital ROSC</p> <ul style="list-style-type: none"> • Presence of a palpable pulse in any vessel for any duration • Sustained ROSC in the field for great than 30s
<p>4. ROSC at Emergency department</p> <ul style="list-style-type: none"> • At ED defined as return of a palpable pulse and measurable blood pressure for at least a minute
<p>5. Any ROSC</p> <ul style="list-style-type: none"> • ROSC at any time during resuscitation, defined as a palpable pulse at any site for any duration • Any return of spontaneous circulation • ROSC regardless of duration. Return of spontaneous circulation (ROSC) meant confirmed palpation of an arterial pulse or recordable blood pressure for any duration associated with an organized rhythm; sustained ROSC meant that these persisted until hospital arrival.
<p>6. ROSC at scene or A and E</p> <ul style="list-style-type: none"> • ROSC at A and E or on scene primary outcome measures were a stable return of spontaneous circulation (ROSC) that has an association with discharge from hospital. This was defined as one being present on arrival in the A&E department or on discharge from the resuscitation room if the patient had suffered a cardiac arrest in the A&E department
<p>7. ROSC > 5 minutes</p> <ul style="list-style-type: none"> • ROSC with blood pressure above 80/50mmHg for at least 5mins (notes that it is different to Utstein)
<p>8. ROSC > 15 minutes (no additional detail)</p>
<p>9. Sustained ROSC >2 hours (no additional detail)</p>
<p>10. ROSC at the end of emergency care (no detail)</p>
<p>11. ROSC before physician arrival</p> <ul style="list-style-type: none"> • Any ROSC before physician arrival. ROSC was assessed by carotid pulse check by firefighters instructed to consider any doubt as absence of a pulse and immediately resume CPR

3.3.2.2. Body structure and function

A measure of body structure or function was included in almost half (n=25: 41.0%) of the studies in this review. In 10 (16.4%) and 21(34.4%) studies body structure or function was reported as primary or secondary outcomes respectively.

57 different outcomes were reported in the domain of body structure and function which were further categorised into sub-domains: circulatory function (9), cerebral function (15); other organ function (12); cardiac rhythm stability (7), respiratory function (6), adverse events (5) and fluid regulation (3). Table 3.6.1 and 3.6.2 details the number of studies reporting each outcome as a primary and secondary outcome and the frequency that each outcome was reproducible.

Outcomes from the domain body structure and outcome were reported with a frequency of 75 reported across the 61 trials. The majority of outcomes were reported on a single occasion. The only outcomes that were measured in the same way or at the same time point on more than one occasion were the termination of ventricular fibrillation (VF) and adverse events.

Despite featuring in 10 studies as primary outcomes the majority of assessments of body structure and function were reported in trials as secondary outcome measures (74.7%). All assessments of body structure and function were completed during hospital stay. Outcomes were most

frequently reported at the following time points; 24 hours (n=26 (23.2%)), during hypothermia (n=22 (19.6%)) and during CPR (n=20 17.9%).

Table 3.6.1: Body structure and function outcomes (table 1 of 2) : Details of different body structure and function outcomes, frequency of reporting as a primary or secondary outcome and the reproducibility of outcome reporting.

Outcome	Frequency reported as a (1) primary outcome or (2) secondary outcome	Frequency of reproducible outcome reporting
Circulatory function		
Blood pressure	(2) 1	0/1
Cardiac index (5 serial measures)	(2) 1	0/1
Heart rate	(2) 1	0/1
MABP (6 serial measures)	(2) 1	0/1
Oxygenation	(2) 1	1/1
Oxygen saturation (3 series)	(2) 1	1/1
Pulse (6 serial measures)	(2) 1	0/1
Systemic vascular resistance (5 serial measures)	(2) 1	0/1
Systolic pressure 15mins after infusion	(2) 1	1/1
Cardiac rhythm stability		
Asystole after study drug admission	(2) 1	1/1
Episodes of VT	(2) 1	1/1
Heart rate variability	(2) 1	1/1
Premature beats	(2) 1	1/1
Satisfactory rhythm on arrival to hospital	(2) 1	1/1
Termination of VF	(2) 3	3/3
Use of vasopressors	(2) 1	1/1
Cerebral function		
Cerebral metabolism	(1) 1	1/1
Cerebral perfusion	(1) 1	1/1
NSE 24 hr after ROSC	(1) 1	1/1
NSE 48 hr after ROSC	(1) 1	1/1
S100 24hr after ROSC	(1) 1	1/1
S100 48hr after ROSC	(1) 1	1/1
S100B at admission	(1) 1	1/1
S100B at 24hrs	(1) 1	1/1
S-NSE at 24hrs	(1) 1	1/1
S-NSE at 48hrs	(1) 1	1/1
S-NSE difference 24-48hrs	(1) 1	1/1
Intracranial pressure	(2) 1	0/1
S100 protein levels day 0	(2) 1	0/1
S100 protein levels day 1	(2) 1	0/1
S100 protein levels day 5	(2) 1	0/1

Table 3.6.2 Body structure and function outcomes (table 2 of 2) : Details of different body structure and function outcomes, frequency of reporting as a primary or secondary outcome and the reproducibility of outcome reporting.

Outcome	Frequency reported as a (1) primary outcome or (2) secondary outcome	Frequency of reproducible outcome reporting
Respiratory function		
Duration on the ventilator	(2) 1	1/1
E _T TCO ₂ 15 mins after drug infusion	(2) 1	1/1
ETCO ₂ (3 series)	(2) 1	1/1
E _T CO ₂ between t10 and t20	(2) 1	1/1
Intrathoracic pressures	(2) 1	1/1
Maximum negative intrathoracic pressure	(1) 1	1/1
Adverse events		
Adverse events	(2) 2	2/2
Adverse events through 24 hrs	(2) 1	0/1
Rate of adverse events	(2) 1	1/1
Rate of complications	(2) 1	1/1
Serious adverse events through day 7	(2) 1	0/1
Fluid regulation		
Capillary leakage	(2) 1	0/1
Fluid administered in first 24hrs	(1) 1	1/1
Total volume of fluids infused	(1) 1	1/1
Other organ function		
Arterial pH	(2) 1	0/1
Creatine kinase (6 serial measures)	(2) 1	0/1
Creatine Kinase MB (6 serial measures)	(2) 1	0/1
Creatinine (6 serial measures)	(2) 1	0/1
Intensity of inflammatory response	(2) 1	1/1
Glucose (6 serial measures)	(2) 1	0/1
Lactate (6 serial measures)	(2) 1	0/1
Organ failure free days	(2) 1	1/1
Platelet count (3 serial measures)	(2) 1	0/1
Pneumonia	(2) 1	1/1
Potassium (6 serial measures)	(2) 1	0/1
White cell count (3 serial measures)	(2) 1	0/1

3.3.2.3. Activities

Assessment of activity limitation was assessed in 52.5% (n=32) of trials focussing on capturing the assessment of neurological outcome and functional status. Activity outcomes were reported more commonly as a secondary outcome on 28 occasions, in comparison to 7 occasions reported as a primary outcome.

Twenty different assessments of activity limitation were described listed in table 3.7. Due to the nature of activity limitation assessment a range of measurement tools were applied to complete assessments. Often activities measurements were described alongside survival. In this report we have discussed combined outcomes purely in the domain of activities, as survival is required to measure activity and some scales for example the Cerebral Performance Category (CPC) and modified Rankin Scale (mRS) incorporate death in the continuum of measurement.

The most frequently reported assessment of activity limitation was the Cerebral Performance Category (CPC) (The Brain Resuscitation Clinical Trial II Study Group, 1991) at hospital discharge (n=14. 23%). A variation of terminology was used to describe this scale with seven (11.4%) additional studies reporting the Glasgow Pittsburgh CPC score. Other measurement tools used to reported outcome of activity limitation included: the Overall Performance Scale (OPC) (The Brain Resuscitation Clinical Trial II Study Group, 1991), Modified Rankin Scale (Bonita and Beaglehole, 1988), Barthel Index (MAHONEY and BARTHEL, 1965) Glasgow Outcome Scale (Jennett

et al., 1981) and location of discharge. The majority of these scales were applied on a single case with the exception of the OPC (n=3) and mRS (n=3).

One study reported assessment of neurological outcome with the application of a tool devised from the Minnesota Living with Heart Failure questionnaire (Rector and Cohn, 2004) and Kansas City Cardiomyopathy Questionnaire. (Green et al., 2000, Aufderheide et al., 2005). Another study reported an interview with patients and family to support the assessment of activity limitation (Breil et al., 2012). These were the only studies that transparently engaged with participants (cardiac arrest survivors) when completing outcome assessments, other assessment is unclear and may have been completed by healthcare professionals, patients or their partners'.

Table 3.7: Activities outcomes: Details of different activities outcomes, frequency of reporting as a primary or secondary outcome and the reproducibility of outcome reporting.

Outcome	Frequency reported as a (1) primary outcome or (2) secondary outcome	Frequency of reproducible outcome reporting
1 year (QOL adapted questionnaire)	(2) 1	0/1
Awake and independent at 3months	(2) 1	1/1
Change in CPC	(2) 1	0/1
CPC 1 week	(2) 1	0/1
CPC 24hrs	(2) 1	0/1
CPC 3 months	(2) 2	0/2
CPC 30 days	(2) 1	0/1
CPC 3years	(2) 1	0/1
CPC at 6 months	(1)1 (2) 4	2/5
CPC at discharge	(1) 2 (2) 12	3/14
Glasgow Pittsburgh CPC at discharge	(2) 7	2/7
GOS 3 months	(2) 1	0/1
Neurological outcome: assessment of notes	(2) 1	0/1
OPC at discharge	(2) 3	1/3
Pittsburgh 6 months	(2) 1	1/1
Survival 1 year with CPC	(2) 1	1/1
Survival and mRS	(1) 3	3/3
Survival free from independence at 6months (BI)	(1) 1	1/1
Survival to discharge with location	(1) 1	1/1
Survival to discharge with CPC 1	(2) 1	0/1

Footnote :BI – Barthel Index(MAHONEY and BARTHEL, 1965), CPC- Cerebral performance category, GOS-Glasgow outcome scale(Jennett et al., 1981), mRS-modified rankin (Bonita and Beaglehole, 1988) and OPC- overall performance category (The Brain Resuscitation Clinical Trial II Study Group, 1991).

3.3.2.4. Health related quality of life and participation

No trials included in this review attempted to capture an assessment of how an individual's health related quality of life or participation in society can be impacted after a cardiac arrest. On one occasion a combination of two PROMs the Minnesota Living with Heart Failure questionnaire (Rector and Cohn, 2004) and Kansas City Cardiomyopathy Questionnaire (Green et al., 2000, Aufderheide et al., 2005) were adapted but applied to measure neurological function rather than health-related quality of life.

3.3.2.5. Processes of care

Process of care were assessed in a small number of studies (26.2%), both as primary and secondary outcomes in 7 and 12 studies respectively. 33 individual outcomes assessments were reported that were further categorised into the following subdomains: cooling devices, quality of CPR, time to treatment or intervention success, duration of stay, specific side adverse effects and long term treatment (Table 3.8.1 and 3.8.2). There was a frequency of 39 outcome reports from this domain across studies.

Outcomes from this domain were most frequently reported referring to the efficiency of cooling devices with 11 different outcomes reported across six studies. Outcomes that were reported in more than one study were: duration of stay in the intensive care unit; CPR compression rate; CPR compression depth; CPR ventilation rates and the time to reach target temperature.

All except one outcome from this domain were reported during hospital stay, one study investigated ICD (implantable cardioverter defibrillator) placement at three years. The majority of the process based outcome measures were reported during CPR (n=12) or during therapeutic hypothermia (n=9).

Table 3.8.1: Process outcomes (Table 1 of 2): Details of different process outcomes, frequency of reporting as a primary or secondary outcome and the reproducibility of outcome reporting.

Outcome	Frequency reported as a (1) primary outcome or (2) secondary outcome	Frequency of reproducible outcome reporting
Cooling device		
Incidence of temperature overshooting during induction	(2)1	1/1
Malfunction of cooling device	(2)1	1/1
Median time to target temperature	(2) 1	1/1
Nasopharyngeal temperature at arrival to ED	(1)1	1/1
Proportion of patients reaching target temperature in 4 hours	(1)1	1/1
Proportion of patients who had temperature out of range during maintenance period	(2) 1	1/1
Temperature at hospital admission	(2) 1	1/1
Temperature at ROSC	(2) 1	1/1
Temperature deviation	(1) 1	1/1
Temperature difference, on ED - randomised	(1) 1	1/1
Time to target temperature	(1) 1 (2) 1	1/2
CPR variables		
Compression depth	(2) 2	1/2
Compression rates	(2) 3	2/3
Compressions with incomplete release	(2) 1	0/1
CPR fraction	(2) 1	0/1
Hands off fraction	(2) 1	1/1
Pauses	(2) 1	1/1
<i>Ventilation rate</i>	(2) 2	1/2

Table 3.8.2: Process outcomes (Table 2 of 2): Details of different process outcomes, frequency of reporting as a primary or secondary outcome and the reproducibility of outcome reporting.

Outcome	Frequency reported as a (1) primary outcome or (2) secondary outcome	Frequency of reproducible outcome reporting
Time to successful treatment or intervention		
1st attempt of vascular access	(1) 1	1/1
Conversion of shocks	(2) 1	1/1
Number of attempts of vascular access	(2) 1	1/1
Number of shocks for sustained ROSC	(2) 1	1/1
Shock success	(1) 1	1/1
Time from defibrillation to ROSC	(2) 1	1/1
Time infusion to extubation	(1) 1	1/1
Time to life support	(2) 1	1/1
Time to ROSC from shock	(2) 1	1/1
Time to successful vascular access	(2) 1	1/1
Total number of attempts to successful vascular access	(2) 1	1/1
Other		
Duration of hospital stay	(2) 1	1/1
Duration on ICU	(2) 2	2/2
Skin lesions	(1) 1	1/1
ICD placement at three years	(2) 2	0/1

3.3.2.6. Time frame of reporting

Outcome measures were reported at various stages of patients' care and recovery, with some measurements being taken before hospital admission, others during hospital stay and some up to three years' post-arrest. Figure 3.2 and Table 3.9 demonstrate the variation of time frame of outcome reporting.

The majority of outcomes (66.5%) were reported before hospital discharge. 22.2% of outcomes were reported at hospital discharge. Long term outcomes were less frequently reported with only 8.5% of outcomes being reported after hospital discharge. A small selection (2.8%) of outcomes reported could not be included in the time frame analysis; this was due to some outcomes not featuring within a certain time frame for all patients or were dependant on the occurrence of an event e.g. regaining consciousness. As figure 3.2 demonstrates hospital discharge was the single time point where measurement was most frequently reported (n=70).

Although a low percentage of survival outcomes were reported after hospital discharge, 46.2% of the outcome measures reported after hospital discharge were survival outcomes. Activity based measurements made up half (50%) of outcome measurements that were completed after hospital discharge. Outcomes reported post hospital discharge were more frequently secondary outcomes (n=21) rather than primary outcomes (n=6).

Figure 3.2: Outcome reporting across the patient journey

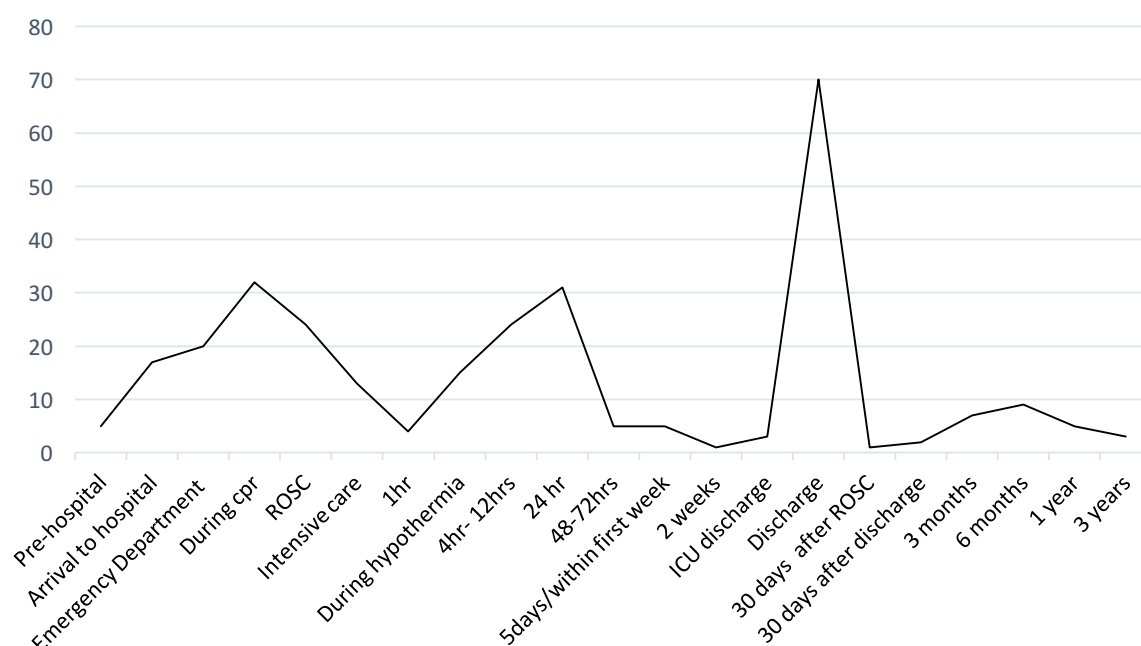


Table 3.9: Distribution of outcome measures before, at and after hospital discharge

Outcomes	Before hospital discharge	At hospital discharge	After hospital discharge
Survival	62 (55.4%)	38 (33.9%)	12 (10.7%)
Body structure and function	112 (100%)	0	0
Activities	2 (4.8%)	32 (66.7%)	14 (29.2%)
Processes of care	23 (95.8%)	0	1 (4.2%)
Total	200 (67.3%)	70(23.6%)	27(9%)

Footnote: 2.2% unidentifiable time points

3.3.2.7. Reproducibility of reporting

Overall 71.1% (263) outcome measures were reproducible. From this 88.6% of the primary outcomes and 67% of secondary outcomes were reproducible (Table 3.10). The lowest reported reproducibility was from activity measures where 35.4% of outcomes were reproducible. Outcomes that were not reproducible lacked detail of outcome measurement including no reference to the measurement tool applied, who completed assessment and how assessment was completed (medical record analysis, observation, face to face discussion or telephone interview).

High percentages of reproducibility were presented by survival and process of care outcomes, displaying reproducibility percentages of 90.2% and 88.9% respectively. The majority of studies reported outcome measures consistently in a reproducible manner with no more than ten (16.3%) studies including more than one outcome measure that was not reproducible.

Table 3.10: Reproducibility of outcome reporting

Outcome domain	Percentage reproducible
Survival	90.2% (111)
Body structure and function	47.3% (53)
Activities	35.4% (17)
Process of care	88.9% (24)
Overall reproducibility	Percentage reproducible
Primary outcome measures	88.6% (64)
Secondary outcome measures	67.0% (138)

3.4. Discussion

Key findings

This review demonstrates the heterogeneity and inconsistencies in outcome reporting in cardiac arrest randomised controlled trials. Variation was displayed in which outcomes were reported, how they were assessed and when they were reported across the patient journey. The absence of guidance for outcome assessment has resulted in a complex and varied outcome selection, emphasising the challenges of choosing appropriate outcome measure to assess a population with a complex nature of recovery.

Across the 61 studies 164 different outcome were reported, with no single outcome reported across all trials. The heterogeneity reported highlights the challenges reviewers would be faced with when drawing conclusions about interventions from a combination of studies. This review expands on the work completed by Trzeciak and colleagues, that demonstrated heterogeneity across studies focussing on post-ROSC interventions (Trzeciak et al., 2009). It also confirms and develops the observations of challenges of heterogeneous outcome reporting reported in reviews of cardiac arrest patients' in specific areas cognitive functioning (Moulaert et al., 2009) and quality of life (Elliott et al., 2011).

An important finding of the review of outcome reporting was the lack of patient centred assessment, with no RCTs included assessing patients' health related quality of life or participation. Only two studies transparently reported communication with patients when completing outcome assessment

(Aufderheide et al., 2005, Breil et al., 2012). Further to this outcome assessment predominantly occurred up to including the time point of hospital discharge. Findings of the review raise concerns whether current RCTs assess the outcome that are the most important and relevant to survivors of cardiac arrest.

Strengths and limitations

This study focussed on randomised controlled trials, assessing outcome reporting across RCTs which are the highest quality of evidence and most likely to influence the care of patients in the future (Grimes and Schulz, 2002). Limiting this review to RCTs also ensured a manageable number of studies were selected for review. The great variation in outcome reporting displayed is likely to be resemble outcome reporting across other types of trials in this field of research. We acknowledge and are aware that in others types of studies such as cohort and observational studies there are still problems with the heterogeneity of outcome reporting but may include different types of outcome assessment. For example a systematic review of quality of life and patient-centred outcomes after cardiac arrest survival which included inception cohort studies, follow up of untreated control groups in RCTs, retrospective cohort studies and case series reported a wide heterogeneity in outcome measurement tools (Elliott et al., 2011).

A data extraction proforma was used to ensure a transparent approach to reporting the challenges seen in outcome reporting. The review was supported by an extensive search including 4 major databases. A limitation

of the studies selected was that the review focussed on English language only publications. No evaluation of the quality and feasibility of outcome measurement was conducted. The purpose of this review was to provide a descriptive analysis of current outcome reporting across cardiac arrest RCTs and to provide a preliminary list of outcome domains for potential inclusion in a COS.

Conclusions

This review demonstrates the large scale of variation in choice of outcome assessment and lack of detailed description of outcome assessment across cardiac arrest randomised controlled trials, raising challenges when comparing the findings of RCTs. In addition to this clinical-based outcome dominance has been shown with a limited assessment of outcome from the patient's perspective. This raises concerns that the outcomes currently included in cardiac arrest randomised controlled trials may not capture the most important outcomes to patients.

Guidance on outcome reporting would seek to reduce the heterogeneity of outcome reporting and promote transparency of methods of assessment. This review supports the development of a core outcome set for cardiac arrest clinical trials to maximise the impact of future research. COS development and successful implementation could result in a standardised approach to reporting.

Chapter 4: Exploring the outcomes that matter to cardiac arrest survivors and their partners: a qualitative exploration

4.1. Introduction

This chapter describes the qualitative interviews conducted with the survivors of cardiac arrest and their partners, which sought to support an exploration of the lived experience of cardiac arrest survivors and the outcomes that really matter to survivors.

Section 4.2 describes a synthesis of previous qualitative research undertaken in this population. Section 4.3 discusses the methodological underpinning to the qualitative research and the conduct of semi-structured interviews. The data analysis and key findings are reported in section 4.4. The chapter closes with a discussion in section 4.5.

Aims:

To explore the lived experience of adult cardiac arrest survivors, the life impact of survival and the health outcomes that really matter to survivors and their partners, from three months after hospital discharge up to the first year post arrest.

4.2. Qualitative evidence

Little is known about the healthcare needs and experiences, or the health outcomes that really matter to cardiac arrest survivors and their partners. Understanding these experiences, values and important outcomes is essential to ensuring that a COS captures outcomes that are relevant to cardiac arrest survivors.

A scoping review of published qualitative literature which sought to identify studies exploring the lived experience of cardiac arrest survivors and/or their partner. The search sought qualitative studies exploring the lived experience of surviving a cardiac arrest, excluded from this were the views of healthcare professionals or partners, studies focussing on the attitudes to resuscitation or the impact of specific treatment (e.g. ICD implantation). Just three of the 70 publications identified in a scoping review explored the lived experience of cardiac arrest survivors (Dougherty et al., 2000, Bremer et al., 2009b, Palacios-Cena et al., 2011) and are critiqued below:

Fifteen survivors of sudden cardiac arrest ((13 men; 2 women; mean age 57 ± 11 (range 31-72 years)) with a Glasgow Coma Score greater than 15 (indicating grossly intact cognition and motor function) were interviewed were interviewed at four points during the first year following their arrest (1, 3, 6, 12 months after hospital admission) (Dougherty et al., 2000). Interviews sought to better understand individuals' concerns, and to utilise this information to inform future nursing interventions. Adopting a grounded theory approach, the following patient concerns were defined: dealing with ICD shocks; emotional challenges; physical changes; activities of daily living; partner relationships and dealing with healthcare providers.

Bremer and colleagues adopted a phenomenological approach in seeking to better understand the impact of a cardiac arrest on patient wellbeing (Bremer et al., 2009b). Nine Swedish survivors of cardiac arrest who had all received an ICD implant (8 males and 1 female age range 44 to 70 years (mean age

unstated); were interviewed between six-months and 15 years after their arrest. Six key themes were described: sudden and elusive threat; awakening in perplexity; the memory gap: a loss of coherence; distressing and joyful understanding; existential insecurity exposed by feelings of vulnerability; and well-being through coherence and meaning in life. The majority of interviews were conducted up to three years post arrest with no further details of time point of interview distribution. A limitation of this study is that long term follow up may impact an individual's ability to accurately recall the impact of cardiac arrest on their well-being during the early stages post arrest.

A group of nine relatively young, non-cognitively impaired, Spanish cardiac arrest survivors (5 males; mean age 40.6 years; range 24-53) ; without cognitive impairment participated in semi-structured interviews (n=19) and completed diary entries (n=5) (Palacios-Cena et al., 2011). Multiple interviews sought to explore their experience of cardiac arrest survival. Four key themes were described: facing fear; the search for meaning; feeling death up close and personal; and loneliness and estrangement. A limitation of this study is that the authors did not report the time-point following cardiac arrest at which the interviews were conducted, hence understanding how these themes may change along the patient journey is not possible and transferability of findings is limited.

The three studies provide a helpful, but limited, insight into the lived experience of cardiac arrest survivors. The studies illustrate the wide-ranging

impact of survival on issues as diverse as emotional impact, fear, spirituality and social well-being. The studies lack understanding of 'what a good outcome, post survival' looks like or the outcomes that really matter to survivors and their partners / carers. Therefore, this phase of the study sought to explore the lived experience of survivors of cardiac arrest and their partners / carers, along the patient journey. An acute episode such as cardiac arrest may have longer term implications once a patient has returned home, therefore it was important to identify outcomes important across the time span of a patients' recovery. Other core outcome set developers should consider the temporality of outcome assessment in the field of interest.

4.3. Methodology and methods

Chapter 2 described several methods that could be adopted to support an exploration of the patients' perspective in understanding the outcomes that really matter to patients. Semi-structured interviews were selected as an appropriate mode of data collection, suiting the needs of the study, the research question and study patient population. Interpretative Phenomenological Analysis (IPA) was selected as a methodological approach to interview conduct and analysis.

4.3.1. Methodology: Interpretative Phenomenological Analysis (IPA)

This section describes the theoretical underpinnings of IPA, summarising the drivers for the growth of IPA in the healthcare arena and the factors that informed the selection of IPA for this qualitative exploration.

IPA is dedicated to an individual's experience of a phenomena and how they understand their experience (Eatough and Smith, 2008). IPA has three theoretical underpinnings: phenomenology, hermeneutics and idiography. These three components are explained below and described in the context of the cardiac arrest population.

4.3.1.1. Phenomenology

Phenomenology is the study of phenomena, describing the understanding of a phenomenon, being or of an experience (Hammond et al., 1991). Edmund Husserl (1859-1938) was the first to describe phenomenology. Husserl explained that experience should be explored on its own and 'going back to things themselves' (Smith et al., 2009). By this Husserl meant separating the experience from additional factors such as personal views and prior experiences, and understanding experience alone. Husserl described how additional factors such as the environment, our previous experience, our consciousness and assumptions can affect our interpretation of phenomena or an experience. Husserl argued that we should look at experience alone by 'bracketing' our preconceptions (Tufford and Newman, 2012).

Heidegger (1889-1976), a student of Husserl further developed the underpinnings of phenomenology, diverging from some of Husserl's views. Heidegger explains that human subjects interact with and are influenced by the objects, individuals, different cultures and the world we live and explains that we are unable to completely isolate our experience of a phenomenon, from the additional phenomena that it occurs alongside (Smith et al., 2009).

Phenomenology and cardiac arrest

In the context of this study, the phenomena that the participant is seeking to understand is their or their partner's cardiac arrest, their survival, and their life after the event. Their interpretation is shaped by previous experiences and living in the world. For example, their experience may be influenced by preconceptions of their health and cardiovascular disease, guided through personal experience or media reporting.

4.3.1.2. Hermeneutics

Hermeneutics describes the theory of interpretation and began with the interpretation of historical and religious texts (Frost, 2011). Although separate phenomenology developments, Heidegger argues that interpretation is essential to phenomenology and understanding experience.

Our interpretation of an experience can be described by hermeneutic cycle considering relationships between factors that may influence interpretation. These factors include previous experience, ideas and assumptions that are continually adjusted with on-going experience (Larkin et al., 2006). In IPA a

double hermeneutic cycle is described. A double hermeneutic cycle exists when analysing data and interpreting the meaning from another person's account. For example, in health research the first cycle represents the participant's interpretation and the second cycle is the researcher's interpretation of the participant's interpretation (Smith et al., 2003).

Although not addressed in IPA methodological guidance, others have described a triple hermeneutic cycle. A triple hermeneutic involves a researcher's interpretation through the account of a research participants' interpretation of somebody else's experience. For example McFarland and colleagues described a triple hermeneutic in an IPA of the views of attendees' of a chronic disease self-management course through interviews of the session tutors (McFarland et al., 2009).

Hermeneutics and cardiac arrest

In the context of interviews conducted as part of the COSCA study, the first hermeneutic cycle relates to a patients' ability to make sense of their experience (that is, surviving a cardiac arrest), based on the integration of previous experience and knowledge with information gathered from the event (the cardiac arrest and recovery). Patients views of cardiac arrest may be influenced by a possible family history or presentation in the media.

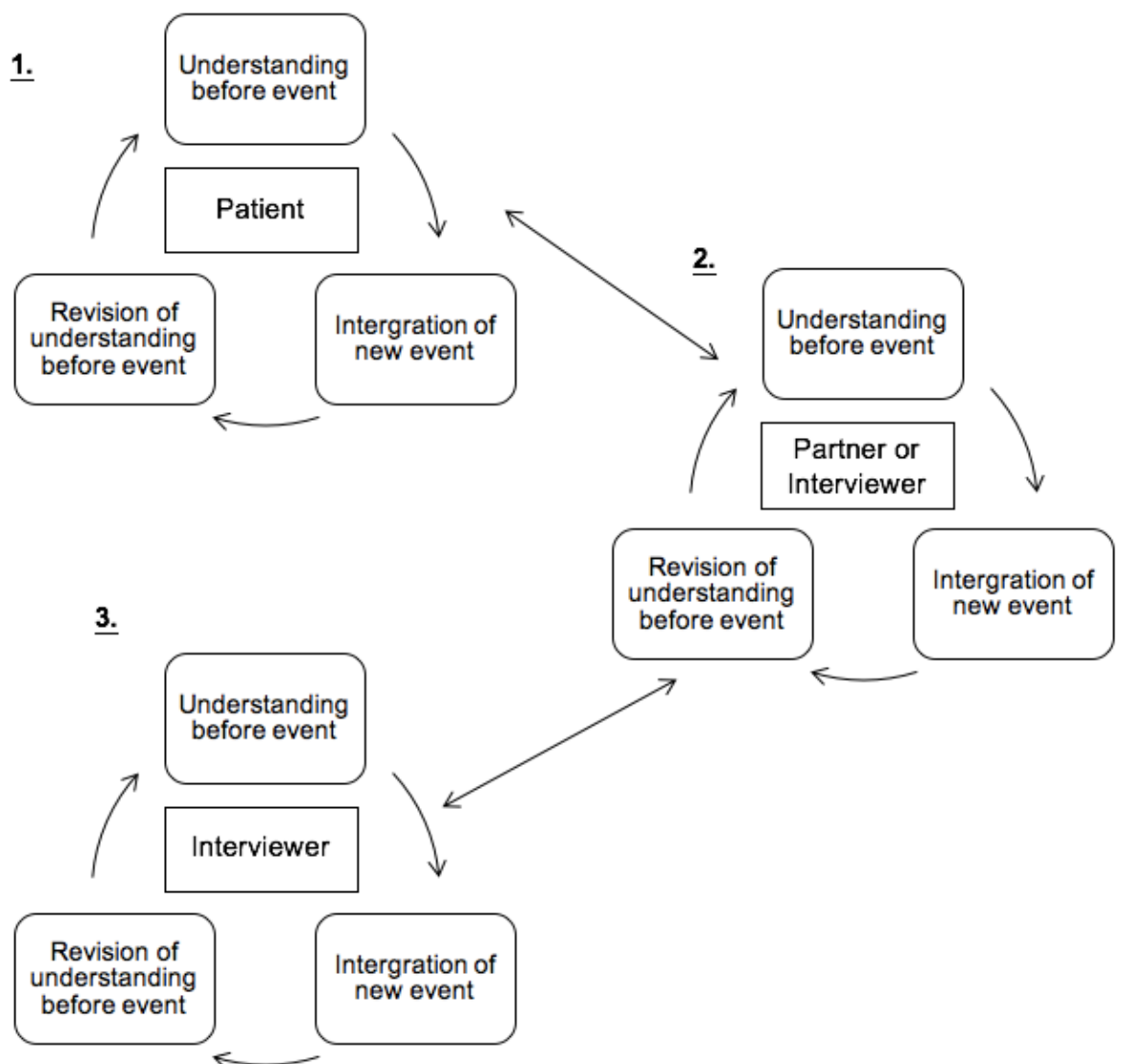
Similarly, a patients' account may be informed by discussion with people present during their cardiac arrest and/or recovery period. Patients lose consciousness during a cardiac arrest and many patients experience

memory gaps prior and after their arrest. Therefore, discussion with significant others may substantially inform the way in which a survivor of cardiac understands and communicates their experiences.

The second hermeneutic cycle describes the researcher's interpretation of the patients' interpretation of their experience. Interpretation may be informed by previous experience and knowledge, interpretation will adjust throughout a study with additional knowledge gained through interview analysis (Smith, 2011). A triple hermeneutic cycle is described with the introduction of patients' partners as participants introducing an additional level of complexity to data interpretation. In partner interviews the content will focus on the patient's experience of surviving and life after a cardiac arrest, the researcher making an interpretation of the partner's account which is based on their interpretation of the patient's experience. A summary of the hermeneutic cycles in the COSCA study is provided in figure 4.1.

Figure 4.1: Triple hermeneutic cycle in the COSCA study

- 1) The patient's (participant) interpretation of the experience
- 2) The researcher's interpretation of the patients' interpretation of the experience or the partner's (participant) interpretation of the patient experience.
- 3) Researcher's interpretation of partner's interpretation of the patient's experience.



Adapted from Course lecture notes: Shaw, R (2013). Introduction to Interpretative Phenomenological Analysis: Theory and Analysis, Aston University

4.3.1.3. Idiography

Idiography is a key component of IPA and describes the study of individuals (Smith, 2015). Meaning that IPA focussed on understanding the particular or individual experience, in comparison to a nomothetic approach which seeks to generalise findings of a wider group (Smith et al., 2009). Due to the commitment to understanding each individual case in depth, IPA study sample sizes are small and in some cases have been single case studies (Smith, 2011).

Idiography and cardiac arrest

The current study sought to develop an understanding of an individual's experience of surviving a cardiac arrest, within the context of their individual lives. Due to the complex and variable outcome after cardiac arrest it was important to understand components of health important to individuals rather than produce an analysis generalizable to this population.

4.3.2. Methods

4.3.2.1. Interview development

Two steps were taken to inform the planning of interviews with survivors of cardiac arrest, firstly observations of home follow up visits and secondly consultation with members of CRAG a patient and public involvement group.

Observation of patient follow up

To inform development of the interview schedule and to gain familiarity with the patient population, the lead researcher (LW) participated in home visits with OHCA patients participating in an existing study with long-term follow-up outcomes (PARAMEDIC - Pre-hospital Randomised Assessment of a Mechanical Compression Device in Cardiac Arrest) (Perkins et al., 2010). During the meeting, patients completed several patient reported outcome measures (including the Short form 12 (SF-12)(Ware et al., 1996), the EuroQol (EQ-5D)(Rabin and de Charro, 2001) and the Hospital Anxiety and Depression Scale (HADs)(Zigmond and Snaith, 1983). It was the perspective of the observer (LW), that patients were happy to talk about their health after their cardiac arrest and to be visited at home. During one visit, the partner of a patient assisted with patient understanding and completion of the PROMs. Thus, highlighting the importance of including the additional perspective of a partner in the proposed research.

Patient and public involvement

During a two-hour group meeting, the lead researcher (LW) explored the design issues for the interviews with an established PPI group: The Clinical Research Ambassador Group (CRAG). Two patients with a history of cardiovascular disease, one with a family history of cardiovascular disease and two of their partners participated in this meeting, the group members were selected to attend the meeting based on their experience of cardiovascular health. Specific advice was sought about: how to approach potential participants, the interview process, the appropriateness of

questions for the interview topic guide and the wording and content of information documents.

An overview of the COSCA study was provided, there was discussion and any questions were answered before asking partners specific study questions. Initial discussions with patient partners indicated confusion of the purpose of the research with partners associating 'outcome' with risk factors and prevention of cardiac arrest, the purpose of the COSCA study were understood after further explanation.

After further discussion with research partners it was agreed that the interview focus of understanding how patients were living their life post arrest, asking questions about how they were feeling and any challenges they were experiences would be helpful for both the researcher and participants whilst minimising confusion, supporting the approach to questioning completed by others (Carr et al., 2003, Keeley et al., 2016). Partners agreed with the approach of the questions listed in the topic guide, no specific comments resulted in changes to the topic guide.

The group suggested that participants should be provided with a choice of interview location – either at their home or at a hospital based location. Information documents were checked for readability and relevance. The information documents were amended to be more concise, with an improved focus on the benefits of participation to future generations.

4.3.2.2. Participants

Inclusion and exclusion criteria

The inclusion and exclusion criteria for patient participants in the interviews are listed below:

- *Survivors of an out of hospital cardiac arrest (OHCA).* In-hospital cardiac arrest survivors (IHCA) were excluded because IHCA survivors are often admitted to hospital due to other illnesses which may mask an individual's ability to consider the impact of CA on their experience and recovery
- *Adult survivors, aged 18 years or older.* A lower age limit was imposed due to the differences in cardiac arrest aetiology and resuscitation care for children (Kleinman et al., 2010). No upper age limit was imposed.
- *Discharged from hospital between 3 and 12 months before the interview date:* This time-frame allowed an exploration of how the experience of OHCA survival changed over time, recognising that aspects of recovery have been reported at and beyond 12-months post OHCA (Raina et al., 2015). Significant improvements in cognitive function have been reported at 3-months post OHCA, but with no further improvement at 6 months (Sauvé et al., 1996a, Sauvé et al., 1996b).
- *Not cognitively impaired and able to self-consent to participate in the study.* It was important that participants were able to participate in interview and hence significant cognitive impairment was an exclusion to participation. Letters were worded so that if patients were

cognitively impaired their partner could complete the interview on their behalf.

- *No serious co-morbidity or terminal illness:* which may influence an individual's ability to consider the way in which their life has been affected by the OHCA.

Or

- *Partners of survivors of cardiac arrest meeting the inclusion criteria above.* An exception of the criteria was made that partners may have been interviewed to explore the view of survivors that were cognitively impaired.

Sample size

Guidance suggests that there is no 'correct number of participants' for an IPA study (Smith et al., 2009). However, sample size should be sufficient to enable an in-depth idiographic interpretation, true to the principles of IPA. A review of 52 IPA-based interview studies in health psychology (1945-2004) described a range of participant numbers from one to 30 (Brocki and Wearden, 2006). Several studies with participant numbers approaching the lower end of this range – between six and ten, have also been described. For example, six participants in a study of suicide bereavement (Smith et al., 2011); seven in studies of macular degeneration (Burton et al., 2013) and multiple sclerosis (Borkoles et al., 2008); eight in a study of chronic fatigue syndrome/myalgic encephalomyelitis (Arroll and Senior, 2008) and nine in a study of benign chronic low back pain (Osborn and Smith, 1998).

Several qualitative studies in cardiovascular disease and resuscitation research have adopted an IPA-based approach, and a wide-ranging number of participants have been described: from a high of 22 patients understanding the beliefs' and cause of myocardial infarction (French et al., 2005); a further study with 9 and 12 patients with different views on attendance cardiac rehabilitation programmes (Wyer et al., 2001); and an exploration of the psychological impacts of implantation of ventricular assisted devices with 6 patients supported by 3 partners (Chapman et al., 2007).

A target sample size of between 7-10 patient participants was therefore considered appropriate to supporting an in-depth ideographic evaluation in OHCA survivors. A target of 7-10 partners of survivors of cardiac arrest was set. No sample size was set for partners of patients without cognitive impairments, this approach was to further develop understanding of the survivors 'experience.

Recruitment

At the time of the interview study a OHCA database of survivors did not exist. Therefore, a convenience sample of OHCA survivors was the most feasible approach to identifying potential interview participants.

Three routes were identified from which patients were sought:

i) Patient registry screening

Two national patient registries – the Intensive care National Audit and Research centre (INARC)(<https://www.icnarc.org>) and the Myocardial

Infarction National Audit Project (MINAP)(Herrett et al., 2010), exist which collect data on patients admitted to UK Intensive Care Units (ICU) and/or patients who have sustained a myocardial infarction. Registries was checked retrospectively and the registry administrator contacted a research nurse when new eligible patients were identified.

ii) Cardiac rehabilitation

The three sites of Heart of England NHS Foundation Trust (Birmingham Heartlands Hospital, Good Hope Hospital and Solihull Hospital) provide cardiac rehabilitation services for a range of cardiovascular patients. The lead clinicians of rehabilitation programmes were contacted by LW to screen for eligible patients attending cardiac rehabilitation classes.

iii) Hospital admission

Birmingham Heartlands Hospital has a strong research focus on the critically ill; research staff screen daily for particular patients admitted to ICU. OHCA patients were included in this screening process. Intensive care admission books at Good Hope Hospitals were checked on weekly basis (by KC a research nurse) for patients whose data may not have been entered onto the intensive care registries.

Approach to patients and partners

Potential participants were approached either via postal mail or on the hospital ward before discharge. For those targeted to receive a mailed letter, General Practitioners were first contacted to confirm patient address and as

a second check on the survival status. A letter of invitation and patient information sheet was developed with the assistance of the CRAG group (Appendix 4.1 and 4.2). Letters were addressed to the survivors of cardiac arrest. However, the letter included an invitation to partners who may be interested in taking part in the interviews. Information documents communicated to participants the status of the researcher and the nature of the project - a University based project supported by the local NHS trust and describe the purpose and nature of the research. The letter advised that, should they be willing to take part in the study to return a form to the lead researcher, alternative contact details (email and telephone number) were provided should they wish to talk about the study more.

For potential participants approached before their discharge from hospital, this followed transfer to a general ward from the intensive care unit and was under the discretion and direction of the ward nurses. Nurses were asked to confirm that patients were sufficiently stable and happy to discuss the research project with the research student (LW). The research student discussed the study with the patient.

Once patients had returned a letter with an interest of participating, a mutually convenient date, time and location to meet for the interview was arranged by telephone call. Once interviews had been arranged with the patients, partners were asked if they were interested to participate and willing to be interviewed on a separate occasion.

Ethical considerations

Ethical approval was received for this study (REC number 13/WM/0464) this study (Appendix 4.3). Participant and research considerations are described.

Participant considerations

Interview studies of a sensitive nature, including discussing surviving a cardiac arrest raise a number of ethical considerations. Firstly, interviews were conducted no earlier than three months after hospital discharge to allow sufficient time for physical and emotional recovery after a cardiac arrest. It was important to explain to the participants the discretion of the interviewer and that published quotes would be anonymised.

It was explained that interviews could be stopped at any time point the participant wished. If a participant became upset, the researcher would pause the audio recorder and give the participant time to compose themselves. Before restarting the interview if willing. The researcher took tissues and support information to the interview in case this may have been of use to the participant.

Researcher considerations

The safety and wellbeing of the researcher was an important consideration; the lone worker policy directive from the University of Warwick was consulted and followed (http://the-sra.org.uk/wp-content/uploads/safety_code_of_practice.pdf). This included informing a study team member designated as a contact point of the location of the

interview, interviewer arrival and completion of the interview. Debriefing meetings were held after interviews with the researcher's supervisor (KH) to reflect on how the interviews went and in case any emotional support was required. Due to the nature of the interviews it was anticipated that interviews could be emotionally draining and stress may be off loaded onto the interviewer so it was important that a debriefing process was in place if necessary.

4.3.2.3. Interview completion

Interview process

At the beginning of the interview the interviewer discussed the study with participants and any questions that participants had were answered. It was reiterated to participants that the interviews would be audio-record and the interviewer may take some notes during the interview to prompt them of discussion points. Participants were advised that the interview could be stopped at any point. After initial explanations and understanding was confirmed, written consent was obtained (Appendix 4.4). Interviews were conducted in private where possible to ensure openness.

Interview topic guide

An interview topic guide (Appendix 4.5) was developed informed by published research with a similar focus (Carr et al., 2003, Sanderson et al., 2010b) and themes identified in the scoping review of published qualitative explorations (Bremer et al., 2009b, Dougherty et al., 2000, Palacios-Cena et al., 2011). The topic guide was discussed for appropriateness with patient

partners. As recommended in IPA, the topic guide was semi-structured (Biggerstaff and Thompson, 2008).

Interviews sought to gain a full picture of the patients' experience, and so patients were asked about the build-up to the event and their health before the cardiac arrest. Although many patients do not recall all their time in hospital, all patients were asked about this part of their experience. Once a better understanding of the context was developed participants were asked more about their return home, the first few weeks at home and their progress since then. The interviews did not follow a specific order, focusing in detail on the key points mentioned by participants. Participants were often prompted to expand on their responses.

Example questions include: "How do you feel about your health now?" "Is there anything that you are looking forward to doing again?" "What would be your biggest achievement since returning home?" and "what advice would you give to others in the same situation?"

At the end of interviews participants were asked if they had anything else they wanted to add in case anything important to them had been missed. The topic guide was adapted in response to interviews, with reflection on topics that participants discussed and questions the interviewer asked which participants needed more guidance and prompt to understand.

Researcher characteristics

Interviews were conducted by the lead researcher (LW) of this study: a 23-year old, female, Caucasian, doctoral researcher with no clinical experience. To avoid over-formalising the interview but maintaining a professional, the interviewer presented herself in a manner that was smart but not overly formal. This was to ensure that the participants felt at ease and open with their responses (Magnusson and Marecek, 2015).

Reflexivity

Immediately after interviews the lead researcher (LW) recorded field notes and initial thoughts. Throughout the conduct and analysis of interviews a reflexive diary was kept.

As a potentially upsetting topic, the lead researcher was prepared for the interviewees to become distressed. However, this was a rare occurrence and partners appeared more emotional than cardiac arrest survivors. The lead researcher felt very welcomed by interview participants and occasionally felt aware of the age gap between her and the interviewees which may have encouraged their helpful attitude.

Where possible transcription and initial reading took place before the next interview in order to allow reflection on interview technique. This highlighted questions that may not have been effective and where further probing may have benefited. The reflection on interview technique was important to

ensure that the interviews were conducted in the best possible way to get the richest data from interview.

4.3.2.4. Interview analysis

Transcription

Transcription was completed by the lead researcher (LW) soon after interviews. This was a step contributing to the immersion in the data and familiarisation with transcripts. Speech was transcribed verbatim without noting stutters. Mannerisms and behavioural responses including long pauses, laughing and hand gestures were noted in brackets. These mannerisms and behavioural responses were noted with the aid of the interviewer completing transcription, this helped further understand the context of the transcript aiding analysis.

Interviews were transcribed within the software programme NVivo (QSR International, 2012) with the advantage of slow speed audio, audio control and transcription in the same window. Transcripts were managed and analysed in Microsoft Word. This allowed for comments to be made on the left and right hand margins of the transcripts and allowed the researcher to work in a way that allowed immersion within the data. All transcripts were anonymised with pseudonyms allocated.

Analysis

Successive steps taken for interview analysis are listed in figure 4.2 (Smith et al., 2009). IPA is a flexible method with analysis being completed on an individual basis before looking for patterns between interviews.

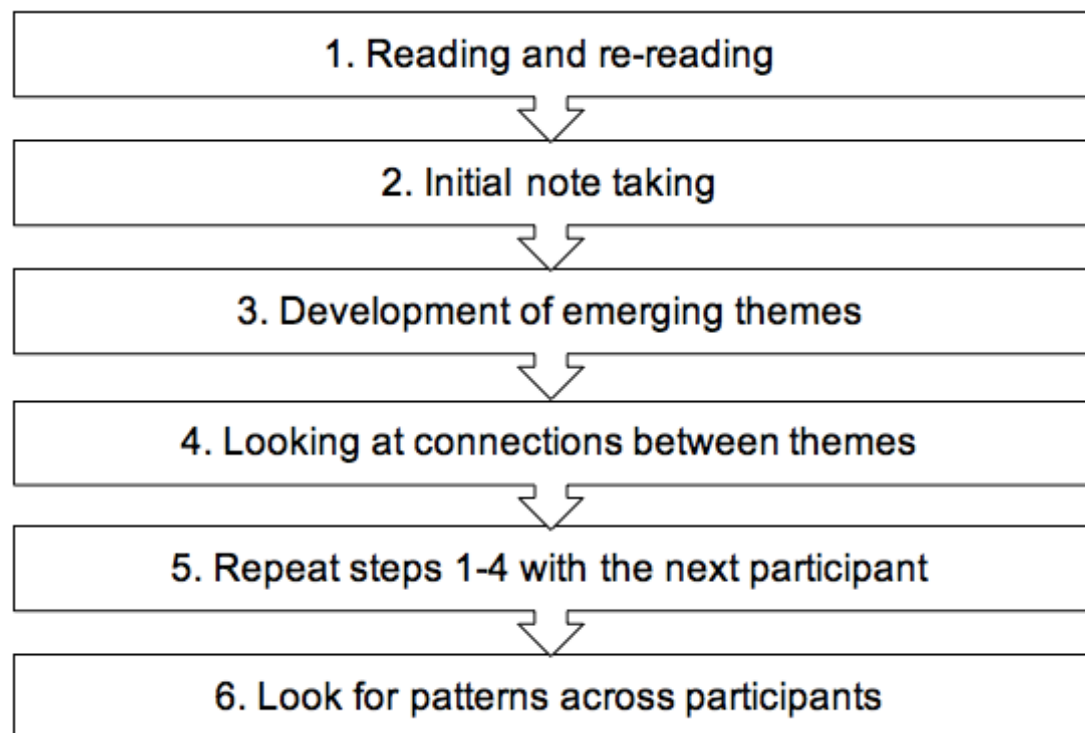
The first stage of analysis was immersion in the data by reading and re-reading the transcript putting the participant's voice at the focus. Initial notes were not made until the transcript had been read several times. Initial notes were taken reflecting both thoughts about the interview transcript detail and separately reflections about interview technique.

Initial notes were made in the left hand margin and were further developed and classified as either: descriptive, based on the description of events and phenomena; conceptual, with some interpretation by what is meant by what the participant is saying or linguistic referring to the language used. These comments were colour coded for each different type of comment. Emergent themes were noted in the right hand margin. In Microsoft Word a table for descriptive, conceptual and linguistic comments were produced, detailing the line number and textual examples. This made it easier to group and find connections between themes.

This was an iterative process that involved renaming and regrouping of themes. Once connections had been sought between the themes of the single transcript, the same procedure was conducted with the next and so on. Once all transcripts had been analysed individually patterns across cases

were explored. Partner interviews further supported the cardiac arrest survivors' interpretation of their experience and emerging themes were compared for any discrepancies.

Figure 4.2: Interview analysis steps



Validation and member checking

No prescriptive process took place for the validation of interview analysis was completed but identified themes were identified by the lead researcher (LW) and discussed and adapted with collaboration during supervisory meetings with KH. In addition to this analysis was supported by Warwick Medical School IPA group. IPA group meetings were attended by other PhD students and researchers with an interest in IPA, with the group led by a Senior Research Fellow (DB) who has a background in psychology and extensive experience in IPA. These meetings provided the opportunity to

share transcripts, ideas and interpretations with others to gain additional view on interpretation, ensuring depth of interpretations and to confirm interpretations were plausible.

Following this point member checking was not conducted, this is where research analysis is taken back to participants to verify data and researcher interpretations (Holloway and Wheeler, 2013). Participants were not consulted about the choice of quotes used or the interpretation of these quotes. Further to this, patient and public involvement may assist qualitative studies in the validation of data, which would introduce an additional hermeneutic cycle for IPA studies. For example, research partners may have a role in checking the researchers' interpretation of data and allocated themes. As IPA acknowledges that it is one person's interpretation of that account member checking and consultation with patient partners was decided against (McConnell-Henry et al., 2011).

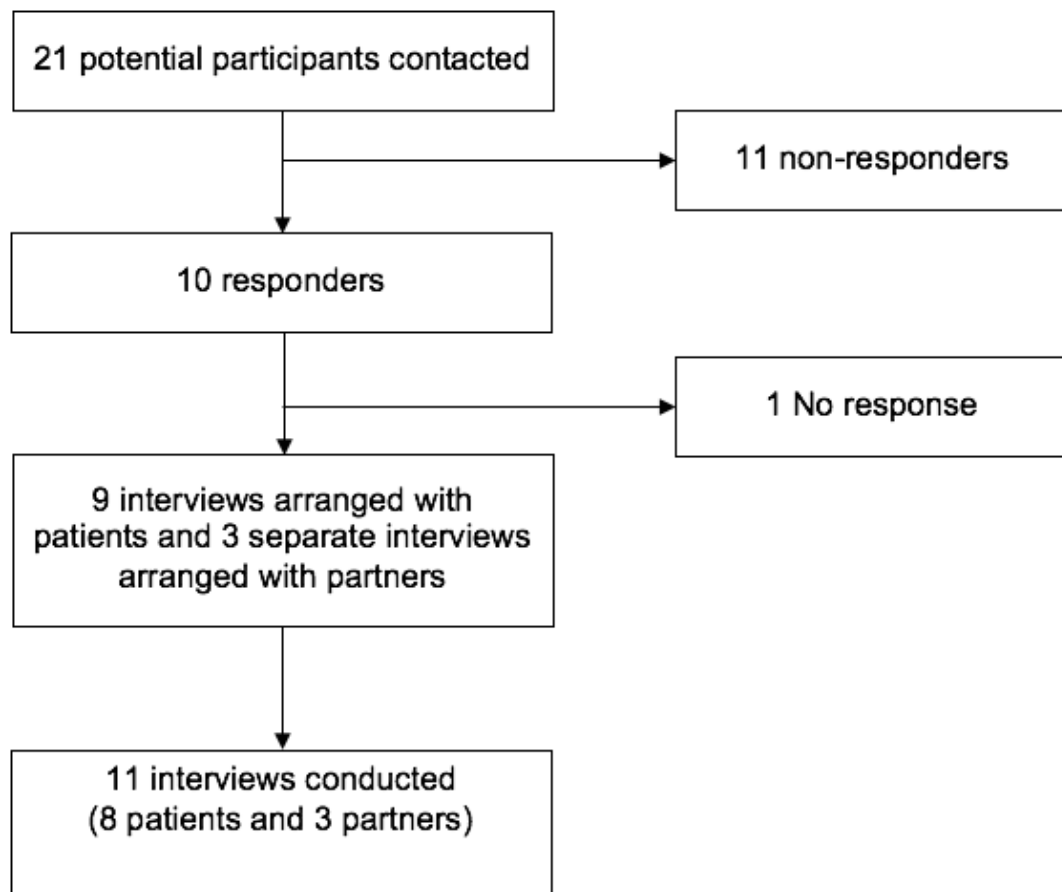
4.4. Results

4.4.1. Recruitment

Twenty-one patients meeting the inclusion criteria were contacted about potential participation in this study. Nine of ten respondents were willing to participate in the study. A total of eight interviews with patients were completed. One interview was arranged but not completed as the patient had changed their mind when the interviewee arrived.

Three of the patients' partners also showed an interest to be involved in the study. Interviews were conducted with three patient's partners on separate occasions. An additional partner was present at the patients interviewed but had experienced a stroke previously, they were consented and welcomed to contribute to the discussion but interviewing was directed towards the patient. One patient was no longer living with his partner so she was not invited to participate. A further three partners did not wish to participate in interviews. In total eleven interviews were conducted over a 5-month period (19.05.14 - 09.10.14). Figure 4.3 illustrates the recruitment process.

Figure 4.3: Patient and partner interview recruitment



4.4.2. Demographic details

This sample was homogenous fitting with the principles of IPA, in that all patients had survived a cardiac arrest in the out of hospital setting and were admitted to hospital from the same NHS trust. A convenience sample of 5 males and 3 female patient participants were aged between 41-79 years (mean age 62.8 (SD:13.6) years). Patients were interviewed at various time points between 3 and 11 months since hospital discharge (mean time point of interview: 6.3 months post-discharge (SD:3.1)). Patients had received a variety of treatments with ICD implantation or stent fitting and one patient having a Coronary Artery Bypass Graft (CABG). At the time point of interviews, two patients had returned to work, one patient was planning to start a phased recovery to work, one patient was unemployed prior to their arrest and four patients were retired prior to their arrest (Table 4.1).

Partner interviews were conducted on separate occasions, following patient interviews by between a week and two months after the initial interview with the patient. Demographic details of partners were not recorded due to the focus of the analysis on the patient surviving the arrest. Two partners interviewed were employed and one was retired. Of the patients whose partners were interviewed two were retired and one was still in employment but working adapted hours, his wife was also still in employment. Of the partners interviewed two were present at the time of the arrest and had provided CPR until the arrival of paramedics.

Table 4.1: Interview cardiac arrest survivor participant demographics

Detail	Interview patients
Age:	41-79 (62.75 SD 13.6)
Gender:	5/8 Male (62.5%)
Work status	Working:2 (1 working same as before, 1 on reduced hours and different role) returning to work on phased recovery :1 Previously retired:4 Previously unemployed:1
Time point of interview since arrest	3-5 months: 4 6-8 months:1 9-12 months: 3 Range 3-11 months Mean: 6.25 months
Treatments	ICDs: 4 (Helen, Kate, Michael Trevor) Stents :2 (Cheryl, David, Henry, Phil) CABG:1 (David)

4.4.3. Interview process

The mean duration of interviews was 42 minutes, with duration ranging from 20 to 66 minutes. Ten interviews were conducted at participants' homes and one interview was conducted in a hospital based location. Interviews were rarely disrupted, some disturbances occurred when pet dogs or children were present. Such disturbances caused minimal impact to audio recordings and all interviews were successfully audio recorded and transcribed.

When both patients and their partner were participants in the study, interviews were arranged on separate occasions and conducted in isolation where possible. One of the patients did not leave the room after both myself and her partner suggested and sat in for the first half of her partner's interview, the second half of the interview felt more relaxed and open. In one interview the partner of a patient had a debilitating illness affecting her speech and mobility and requiring care. In this interview the questions were directed at the patient and the partner was encouraged to contribute anything they wished and their consent was obtained. As this was not a detailed patient account this was not considered as a separate partner interview.

4.4.4. Pen portraits

Listed below are pen portraits of each interview participant providing a background to each participant as an individual:

1a. David, 58 (9 months after hospital discharge)

David was swimming at the time of his arrest. He required a coronary artery bypass after his cardiac arrest, this was complicated by a transient ischaemic attack, affecting vision in one eye. David was very keen to get back to swimming and had returned to work on reduced hours in an adapted role. David felt that his recovery had taken longer than expected as he was in good health before and felt let down that doctors kept telling him he would be a 'New man.'

1b. Celia, David's wife (11 months after hospital discharge)

Talking to Celia emphasised some of the key symptoms David talked about and enforcing how much he really wanted to get back to 'normal'. Speaking to Celia also highlighted the impact on the family.

2. Helen, 79 (7 months after hospital discharge)

Helen had her cardiac arrest after going to the shops and was resuscitated by her partner. Helen was previously widowed, and had lost family members (children) through cardiovascular disease. She had increased dependency after her arrest and had a loss of interest in some of her hobbies. Helen displayed some indication of detachment from the event. Following her cardiac arrest, Helen had stopped smoking and saw this as positive change to health.

3. Henry, 52 (11 months after hospital discharge)

Henry had his cardiac arrest at the local shops. Henry was satisfied with his recovery and found that others were more worried than him. He was eager to get back to work and is now working more than before. Henry didn't see himself as a 'typical' cardiac arrest patient. At the time of interview Henry was living in a new flat after a recent separation.

4a. Cheryl, 64 (4 months after hospital discharge)

Cheryl had her cardiac arrest whilst out and was resuscitated by her partner. Cheryl was retired prior to her cardiac arrest. She was aware that she needed to make changes to her lifestyle by increasing physical activity and improving her diet. A difficult part of Cheryl's early recovery was the pain from broken ribs from CPR. Cheryl found the number of tablets she had to take frustrating.

4b. Gary, Cheryl's husband (4-5 months after hospital discharge)

Gary began resuscitation when Cheryl arrested. This wasn't the first time Gary had performed CPR but explained it was a very different experience to resuscitating his wife and he was relieved when the paramedics arrived. Gary still works whilst Cheryl was retired prior to her arrest. Gary explained how the event had affected Cheryl's confidence and his own.

5. Paul, 56 (3 months after hospital discharge)

Paul's cardiac arrest happened whilst he was driving home from a charity run. He was helped by passers-by. At the time of interview Paul was about to

start a phased return to work as a civil servant. Paul lived at home with his wife and children. Paul was concerned about his memory and ability to do his job. He had previous cardiac episodes and frequently made numerous references to having a healthy diet.

6a. Michael, 79 (9 months after hospital discharge)

Michael's cardiac arrest happened when he was sleeping at home and he was resuscitated by his wife. Michael had some other health complications in hospital and rearrested more than once. Michael appeared to have some memory of when he arrested again. Michael was extremely appreciative of his wife caring for him and felt that she was not given the necessary support. Michael found he was weaker than before, affecting some of his hobbies.

6b. Karen, Michael's wife (10 months after hospital discharge)

Karen began resuscitation on her husband Michael. She described how it was difficult when Michael returned home and she did not believe that she had sufficient support. Karen highlighted some changes seen in Michael's personality and cognition.

7. Kate, 41 (3 months after hospital discharge)

Kate's arrest happened at home and was found by her daughter who sought help from a neighbour. Kate explained how she had experienced anxiety before her arrest which had improved since her arrest but was beginning to return to pre-arrest level.

8. Trevor, 73 (3 months after hospital discharge)

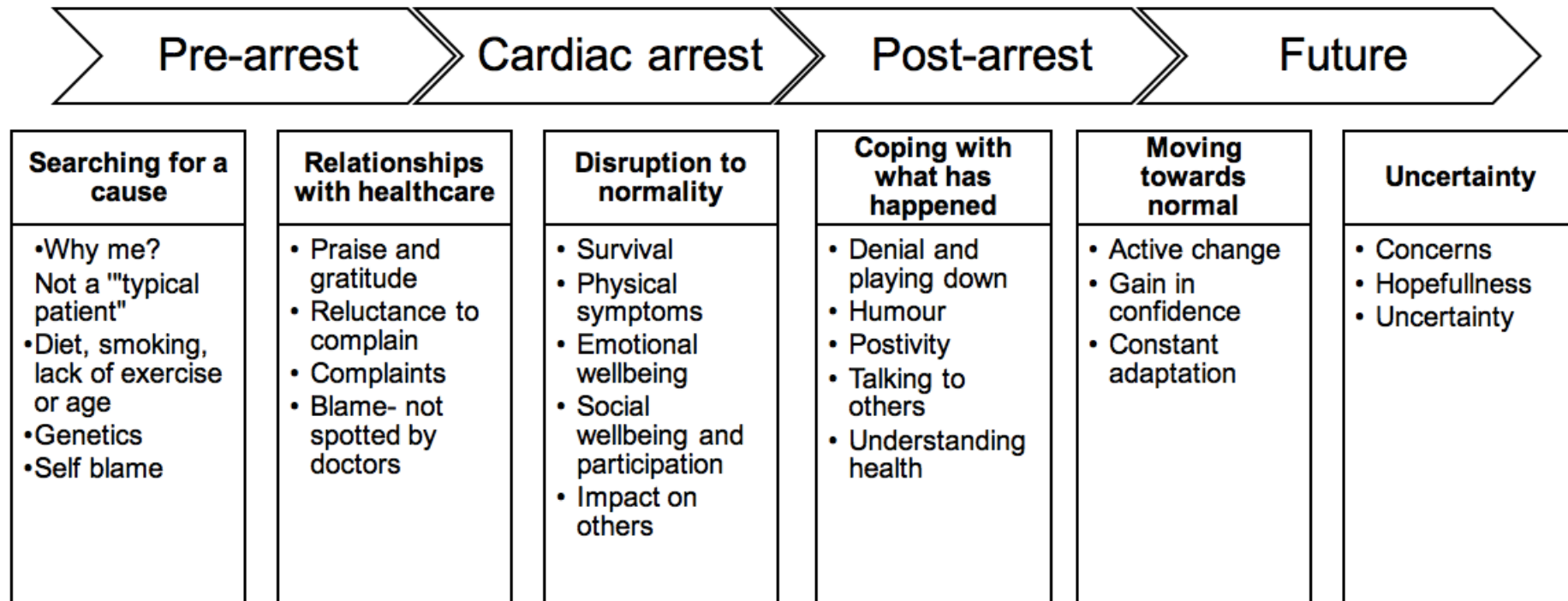
Trevor arrested after shopping and was helped by passers-by. Trevor made a good recovery and explained that his family made him a journal whilst he was in hospital which he sometimes reread over. Trevor's wife also sat in on the interview and was consented for the recording and transcription of data, questions were directed at Paul and his wife was encouraged to add anything she wanted. Trevor's wife had a stroke some years ago and he was able to care for her with minimum help. Since his arrest carers come to the home more often and he cannot take her to a day centre she used to attend.

4.4.5. Themes

4.4.5.1. Superordinate themes: The broader picture

Understanding the lived experience of surviving a cardiac arrest is crucial to this research. Each patient told stories of their recovery with commonalities between interviews, alongside components unique to each participant's story. The stories displayed a timeline of key time points, with reflection on their pre-arrest health, the sudden event of a cardiac arrest, their recovery focussing on getting back to normal and the uncertain future. Across the patient journey the following themes were identified: disruption to normality, coping with what has happened, getting back to normal, the uncertainty of the future and their relationship with healthcare. These themes across the patient journey are illustrated in figure 4.4.

Figure 4.4: Overview of superordinate themes across the patient journey



All participants described changes after their cardiac arrest presenting as new symptoms causing “disruption to their normality”. Participants displayed a variety of different coping mechanisms to come to terms with what happened to them. For example, some may have been playing down their symptoms, found comfort in humour and others tried to find a cause for what happened to them. Many participants took an active approach towards getting back to normal, feeling that it was their responsibility to improve their health in order to prolong their life. Participants described an ongoing adaptation and trying to move towards normal. Although interviewees were hopeful and positive about their recovery they indicated underlying concerns and uncertainties about the future.

The superordinate theme a disruption to normality conveys the symptoms and the health outcomes that are the most important to cardiac arrest survivors; therefore, it is the focus of this thesis since it fits most closely with its aims. Other superordinate themes were important contributors to the patients’ recovery and are planned to be written up elsewhere.

4.4.5.2. Superordinate theme: Disruption to normality

Survivors of a cardiac arrest are faced with many new symptoms and their impact that demonstrated a disruption to normality. These disruptions to normality can be further grouped into the subordinate themes of: survival, physical function, emotional well-being, social well-being and participation and the impact on others. These subordinate themes are summarised in table 4.2 and discussed in further detail with supporting quotes next.

Table 4.2: Overview of the superordinate theme disruption to normality, superordinate themes and examples.

<i>Superordinate theme</i>	<i>Subordinate themes</i>	<i>Examples</i>
Disruption to normality	Survival	Closeness to death Gratitude to be alive
	Physical function	Fatigue Breathlessness Vision Muscle weakness Pain (<i>rib break</i>) Activities of daily living/increased dependence Cognitive function
	Emotional well-being	Anxiety Confidence Depression Self esteem Personality changes Frustration
	Social well-being and participation	Participation (role: job, voluntary, carer) Participation (leisure: hobbies, sports) Participation (social activities) Participation (family: relationships)
	The impact on others	Increased work/care Impact to their participation – hobbies, work Strain on relationships worry

4.4.5.2.1. Subordinate theme: Survival

Survival was highlighted as an important outcome domain. Participants indicated awareness that there was a period when their life was at threat and their closeness to death. Others demonstrated the importance of survival by describing their gratitude to be alive resulting from the help of others. Some survivors displayed a change in outlook on life with one participant describing how you've got to make the most of life and another describing how he was less affected by certain things because there 'is more to life'.

"But it's quite catastrophic when I had the second heart attack because there just was no blood at all."

David Interview 1a

"And I thought that was a big help to somebody who's thinking they've been at deaths door, which I had and she's there fully understanding the way I feel and I think that's nice, that's nice reassuring you."

Michael Interview 6a

"Because without that you wouldn't be here you've got to, to do things you know it's not the end you're lucky you're still here and you've got to do something with it."

Cheryl Interview 4a

4.4.5.2.2. Subordinate theme: Physical function

All participants described new physical symptoms resulting from their cardiac arrest that had an impact on their daily life. Some symptoms were more common across interviews including: fatigue, breathlessness, muscle weakness and cognitive impairments. Less common symptoms resulted as side effects of treatments such as impaired vision and pain from broken a ribs. Many participants talked about how these symptoms made activities of their daily life were more difficult than before, making them more dependent on others.

Fatigue was often described as a new tiredness experienced from doing very little, having affects mentally and physically. This tiredness was something they hadn't experienced before. It would come on suddenly and had an impact on daily life.

"Indirectly, one thing I wasn't prepared for was how tired I would be at the time and so you know it's self-limiting. Whereas before I'd go out with friends and stuff, sort of drink rather more than should do, now you know come 9 o'clock I am ready for bed (laughs)."

David Interview 1a

"I just, my brain just goes. It's like as if it goes to sleep and body goes eowwww. I just need I just need to lie down. It's just comes all of a sudden you know, it isn't something that builds up and I think oh I'm getting a bit

tired but for me it just happens.”

Cheryl Interview 4a

Some participants described how increased breathlessness made completing physical activities like walking, climbing the stairs and exercise difficult. This meant they would have to take more regular breaks and need to make adjustments in activities.

“When I first came out of hospital I applied for a blue badge and they gave me one because I couldn't walk ten yards...so that is extremely useful and I don't like stairs. Stairs I find very ugly.”

Michael Interview 6a

“If I go upstairs I feel like I've run round the block. I do get out of breath quick but I don't know if that's smoking...”

Kate Interview 7

Some patients described a loss of weight and muscle strength, which may be contributed from long periods of inactivity and time in hospital. Sometimes as a result patients adapted their leisure activities.

“From the bedroom to up here and back to the bedroom and that is really how frail he was. He was extremely frail, he lost a hell of a lot of weight and he lost muscle strength. And his legs were like spindles.”

Karen Interview 6b

“Cycling is another one, I just don’t have the strength in my legs at the moment to even make it worthwhile, to get on a bike at all, I’m going to change that in a couple of weeks’ time.”

David Interview 1a

Participants often saw an impact on their ability to complete activities of daily living resulting in an increased dependence on others. Activities of daily living included housework, gardening, carrying shopping and driving. Many found themselves more dependent on others than before their cardiac arrest and for some a contributor to this was not being able to drive until at least six months after their cardiac arrest.

“At the end of the day and I mean it’s not as if I’ve got to do it all myself, I haven’t. I don’t carry the shopping, (Partner’s name) will say leave that we just work it between us... Oh yes he’s definitely done more since oh yeah.”

Helen Interview 2

“I find certain things, simple things like stripping my bed and making the bed back up.....It’s more of an effort, I used to be able to do it on my own, I could do it but I do need a bit of help but that is getting better than it was you know.”

Cheryl Interview 4a

Participants explained some symptoms resulting from side effects of treatment. These side effects included pain from ribs broken during CPR, a loss of visions and problems associated with ICD's a device implanted that can provide shocks if necessary.

"The worst part about it all, was my husband and the paramedics gave me CPR and between them all they cracked about four of my ribs. And that was the worst pain of all."

Cheryl Interview 4a

"All of a sudden we heard and it sounded like an ambulance in the distance I thought oh my whats that. And I realised it was coming from (patient's nickname) chest and the nurse, I swear to god she changed colour and she scarpered quick."

Karen Interview 6

Symptoms of disruption to cognitive function were referred to often in interviews. This impact to cognition can affect: memory, executive function, attention, concentration or linguistic function.

Most participants could not remember parts of their cardiac arrest event, which is expected due to periods of unconsciousness. However, they described problems with their memory once returning home of recent events

or memory of things prior to their arrest. These symptoms could cause embarrassment, concerns and frustrations. Several participants described word ataxia, where they often struggled to say the words they wanted to.

“The cognitive nurses came in two or three times and we went through various card games in effect... Where you get a tray and you get items on it covered over and you uncover it... Which is a wizzard game as a kid and when your an adult you think what the bloody hell is on that tray. It it's almost, well it's not almost it is embarassing because you think, I'm fairly intelligent and I can't remember what is on this tray.”

Paul Interview 5

“I do lose my memory and I don't know, that's what scares me the most.”

Kate Interview 7

“Somebody will ask me the name of something and I can't figure what it is and I'll remember it but it'll be the wrong one, you know I'll get it all twisted and it'll be something totally different that's about it.”

Helen Interview 2

Participants described how their cognitive function made it more difficult to make decisions and retain attention. In some instances, this had affected an individual's ability to complete their job role.

“On the mental side I noticed that the decision making at the moment is just not there. I think this is probably out of practice whereas before if you’re on the phone you’d just make decisions as you’re on the phone now there’s that “ummm” thought think time which of course you can’t have in a telephone conversation with clients.”

David Interview 1a

4.4.5.2.3. Subordinate theme: Emotional wellbeing

Disruption in emotional well-being was indicated by participants displaying: anxiety, a lack of confidence, low self-esteem and some depressive symptoms. The majority of participants had many frustrations after their cardiac arrest, which impacted their emotional well-being. From interviews with partners’ low confidence and changes in personalities were highlighted as changes since the cardiac arrest.

Some explained symptoms of anxiety and worried that they could arrest again.

“I have moments when I sit thinking, am I having a pain in my chest is this because I've been exerting myself. Should I be thinking more carefully about what I should be doing or does this happen to everybody and I'm now a little paranoid about what happens.”

Paul interview 5

"It is it scary, I'm scared incase it happens again aint it. I cant get to sleep because Im thinkng Im not going to wake up."

Kate interview 7

Confidence was not identified as important from patient interviews, however partners described the patients' confidence improving over time with their daily activities beginning to return to a resemblance before the cardiac arrest. In addition to this once necessary procedures were completed this gave patients further reassurance.

"His confidence has grown. I think it was quite frightening for quite a long time. The fact that he got no warning and because he had no pain no warning how'd do you known it wouldn't happen again."

Celia Interview 1b

"She's had the stent fitted and she's sort of a lot more confident and she realises she can push herself."

Gary Interview 4b

A less apparent disruption linked to confidence was a lack of self-esteem. This was indicated by patients where they questioned their roles and identity since having a cardiac arrest with changing the way they the saw themselves and how other people saw them.

"I took to walking round with a little bag like a duffle bag which you got a bottle of water in and my drugs and all the rest of it. Because then if you've got a bottle of water you're allowed to sit down on any bench and have a drink and get your breath back but we will keep that bit quiet. And finding that you're short of breath, that's not a nice feeling you."

Paul Interview 5

"I don't like people to treat me as an invalid and they do, my family do my kids do you know. Ohhh dont do that. It's it's soul destroying, well what the hell am I here for then (laughs). It really is but there you go, best intentions."

Michael interview 6a

Increased frustration was experienced by some patients. Many different things caused the participants frustrations; however, most of this frustration stemmed from the physical, mental/cognitive and social limitations resulting from their cardiac arrests stopping them from doing certain things or others not allowing them to do things they previously would have.

"...it does get frustrating when you think to yourself I really haven't done enough work to or anything like anything done anything really to feel this tired."

Cheryl Interview 4a

“And that I find a little difficult, cause I've been doing it for probably twenty years and I CAN'T. I'm told to do it because they wont' allow me to do it the the care workers.” (As a result of Trevor's cardiac arrest he needed help from carers to care for his wife).

Trevor Interview 8

Interviews with partners described some changes in personality of the patient since their cardiac arrest. One person indicated that the patient had lower level of patience and another that the patient was more withdrawn than before.

“He's very inpatient now, he gets more impatient with people, situations, definitely got a shorted fuse that he did have.”

Karen Interview 6b

“You know but it's like where he might have been chatty before he's a bit more silent than he was. I don't know whether that's a normal thing?”

Celia interview 1b

Participants were open about their emotional recovery, explaining how they were more emotional than before. Many explained an 'up and down' process indicating some depressive symptoms whether this was feeling down, upset or losing interest in hobbies. They had explained how they had discussed this with their partner's.

“Erm I have me ups and downs after it first happened and when I came home, I'm not the sort of person who cries that easily but anything could trigger me off crying and my sister just look at me and say that's just not you and I'd say well I can't help it but that's a lot better now.”

Cheryl Interview 4

“I did a lot of craft work like these and dolls houses I haven't got the same, I don't feel the same. I don't know why it's just disappeared I know it sounds daft.”

Helen Interview 2

“Well I started to get depressed. I mean I didn't tell anybody but I got Karen might a I got out the shower one day and I just broke down in tears and everything but Karen didn't know but she did come in and find me in tears and that just happens occasionally.”

Michael Interview 6a

4.4.5.2.4. Subordinate theme: Social wellbeing and participation

The physical, cognitive and emotional described influenced patients' social life in a number of ways; it affected roles, whether these were in paid employment, voluntary, as a carer or within the family. Patients socialised less or were less able to participate in leisure activities.

Three participants were in full time employment at the time of their cardiac arrest. When the interviews took place they were at different stages of their return to employment. Phil was about to start a phased return to work after at least 3 months off, David had been back a couple of months 12 months since his cardiac arrest on reduced hours and an adapted role in comparison to before his arrest. Henry was eager to get back to work and has found himself working more than ever. None of those in employment had decided to take early retirement.

Paid employment was not the only role effected. One participant described that how his role as carer had changed since having his cardiac arrest as he was no longer allowed to life his wife who required care. No participants described inabilities to complete their roles within the family context but indicated power shifts and role reversals due to increased dependence on relatives. This was more prominent in interviews with children still education.

“And they said that’s not on now. You’ve got to have two carers and we will do the work of what you’ve been doing (re: lifting wife).”

Trevor interview 8

“It’s a bit weird with your kids coming to see you in the hospital and your family because they think they see more of an issue than I did. They should have been the ones being looked after.”

Henry interview 3

Participants described how they were unable to do some hobbies that they did before their cardiac arrest either at all or as much as they liked; these included sports, gardening or work on cars. Furthermore, some described how they found socialising more tiring than before, having to make adjustments and not making as many plans.

“He could not wait to back swimming again, he really couldn't wait and he was very disappointed when the doctor told him he couldn't.”

Celia interview 1b

“He can't, he can't do things at the allotment anymore like he used to. He's still he's still got it I would like him to give up the allotment if I'm quite honest.”

Karen interview 6b

4.4.5.2.5. Subordinate theme: Impact to others

It was clear that although the patient has had a direct disruption to their health this can have a great impact on those around them which patients feel responsible for. A cardiac arrest can result in a change in routines for family members, increased anxiety for family members and also put strains on relationships. This came across in the majority of interviews and was not isolated to the cases where the partners of patients were interviewed, although these participants may have been more aware of this impact.

Some described how their cardiac arrest had an impact on their partner's daily activities, social activities and an increased workload for their partners.

"Now during the day (partner's name) used to go to a day centre....But we are snookered a bit with the transport to begin with (pause).

No I don't think our lifestyle is still apart from that we haven't."

Trevor Interview 8

Others explained how the cardiac arrest could cause emotional stress, anxiety and worry for their family members which could also put strain on relationships. For some these included their partners caring for the patient but also the concerns of their children.

"He will admit now that he has found it really, really stressful. (Pause)

He doesn't give in very often; he has found it really stressful in the fact that he's just worried."

Cheryl Interview 4a

"I think it's the one is the impact on your family because I felt fine maybe I'm different but the effect on my boys and they were really worried and panicked and all the rest of it."

Henry interview 3

"I think it was more stressful for (partner's name) than it was for me. In as much as when I was in hospital I was being looking after and I couldn't be

looked after better but when I came home the responsibility went straight back onto her shoulders and we don't, I don't, we didn't get the support I didn't think from the community nursing that she deserved."

Michael interview 6a

"I've said my wife has made numerous references to me not having done things."

Paul interview 5

4.5. Discussion

Key findings

This is the first qualitative exploration with survivors of cardiac arrest and their partners to better understand the lived experience of survival and the health outcomes that really matter. Interviews highlighted patients surviving a cardiac arrest has a disruption to their normal health describing changes to: survival; physical symptoms; emotional well-being, social well-being and participation and the impact.

The disruption to normality described by authors, may be applied to the concept of 'biographical disruption'(Bury, 1982). Similarly, this study described changes to view on self and their understanding of daily living. Survivors of cardiac arrest experienced a sudden threat to their previously perceived healthy life with many patients not seeing themselves as 'typical cardiac arrest patients'. As a result of the arrest patients experienced new symptoms and their wider impact to daily activities and social interactions. Patients saw their pre-arrest status as an optimum way of being, against which they judged their current health and recovery.

Participants demonstrated variable degree of impact resulting from their cardiac arrest on their daily lives. Reviewing the time point of interview after hospital discharge there were no observed relationships between impact and length of time since hospital discharge. Some participants interviewed soon after (3-4 months) hospital discharge displayed less difficulties with their recovery in comparison to those close to a year after hospital discharge.

This may have been observed resulting from stages of denial in initial stages of recovery (Dougherty, 1994). Outcomes were important to patients once they had been at home for some time and were working towards getting back to normal, with most patients having limited recall of what happened in hospital, conversely in current RCTs measurement is focussed to the time points during hospital and at hospital discharge.

New physical symptoms after cardiac arrest included: fatigue, breathlessness, muscle weakness and cognitive function. Further to this the qualitative interviews highlighted the importance of emotional well-being, social well-being and participation and the impact on others for survivors; but these concepts are not currently assessed in published randomised controlled trials. Current reporting in RCTs fails to report outcomes that are the most important to patients surviving a cardiac arrest.

Interview with patients and their partners' highlighted the importance of seeking to better understand the patient experiences and the outcomes that matter to the most to patients. This is an important stage to identifying potential outcome domains in COS development, identifying gaps in current outcome reporting.

The themes and outcomes important survivors of cardiac arrest are can be applied frameworks described in the introduction: The Wilson and Cleary framework, the ICF framework and the OMERACT filter 2.0. Themes fit within the Wilson and Cleary framework, highlighting the importance of new

symptoms, their impact on functional status and perceptions of health. There was a lesser focus on outcomes important to patients from the domains body structure and function from the ICF framework. Many of the themes reported were from the OMERACT 2.0 filter core area life impact. Further to this the appropriateness of the OMERACT 2.0 filter supported the classification of survival.

Key findings in the context of other research

Each health domain identified in interviews contributing to a disruption to normality will be discussed briefly in the context of other research.

The identification of survival as an important outcome is supported by its wide reporting in clinical trials but this is also supported by qualitative research with patients. Others have identified themes of survival in patient interviews being described as ‘feeling death up close and personal’ (Palacios-Cena et al., 2011) and as a ‘sudden and elusive threat to life’(Bremer et al., 2009b). Survival was unquestionably important to patients but they were aware of the seriousness of their cardiac arrest event with many indicating gratitude to those that helped them survive.

A similar study completed to understand the concerns of myocardial infarction (MI) survivors (with ICD implantation) reported changes in physical function and activities of daily life after cardiac arrest (Dougherty et al., 2000). Similar commonly described symptoms were fatigue, memory loss and the limitations of physical stamina. This study further expands the

importance of these symptoms that may be experienced after cardiac arrest and their wider impact. For example, further expanding on the cognitive implications after cardiac arrest, interview participants in this study described challenges with decision making and mild aphasia- finding difficulty to express the correct words and how these can have a wider impact on completing daily tasks and working roles. Another example, was the wider impact of physical symptom and reduced activities of daily living resulting in new limitations having an impact on employment, voluntary roles, leisure activities, hobbies and socialisation.

Other qualitative work has limited discussion about how symptoms resulting from a cardiac arrest can widely affect social well-being and participation. New symptoms did not just affect individuals' employment but voluntary roles, leisure activities, hobbies, socialisation and their relationship with their partners for some participants. No RCTs in the review in chapter three reported at the impact of cardiac arrest on participation but a number of observational studies have explored how this may effect participation in roles. Retrospective studies have indicated variable return to work rates which is a strong indicator of normality for survivors. One study has indicated 78% of a sample of OHCA survivors returning to work within 1 year (Kragholm et al., 2013). This study is strengthened but the consideration of factors such as sick leave and their ability to complete their job role as identified in interviews once back at work survivors faced challenges. In an older and smaller study, Sunnerhagen and colleagues reported how almost 60% of OHCA were not back at work 17-40 months post arrest

(Sunnerhagen et al., 1996). Another study described much lower return to employment rates of 13% after 1 year (Lundgren-Nilsson et al., 2005), however this study was conducted with a smaller and older population of survivors. A limitation of these studies is the duration of follow up, it is unclear at what time point survivors return to work and a year off work may not be feasible to support their family, in the UK patients are advised that they should be able to return to employment approximately three months.

Other than participation in the context of paid employment it has been reported that a large number of cardiac arrest survivor participation more generally is affected. A study of 63 survivors indicated that 74% of these had low participation in comparison to the general population (Community integration questionnaire) (Wachelder et al., 2009). Socialisation and participation in sporting activities were important changes described in this study.

Similar aspects of the impact of a cardiac arrest on others was described by Bremer and colleagues at the 'overwhelming responsibility' patients partners are faced with upon returning home from hospital (Bremer et al., 2009a). A quantitative observation noted that 17% of partners score high levels of strain (Caregiver strain) (Wachelder et al., 2009). This area of healthcare needs greater focus, providing better support to partners.

Further to the themes discussed in this thesis contributing to 'a disruption to normality,' the following themes contributed to the lived experience of

surviving a cardiac arrest: coping with what has happened, getting back to normal, the uncertainty of the future and their relationship with healthcare. These themes will be presented in depth a future time point. Since the conduct of this study, Ketilsdottir and colleagues published a similar study of seven male survivors of cardiac arrest, without ICD implantation, aged 50-54 to understand the experience of surviving a cardiac arrest (Ketilsdottir et al., 2014). Themes identified further support those identified in the COSCA study relating to dealing with their sudden change to their life and health, including: feelings of insecurity and the need to support; striving to regain former life; emotional challenges; responding to new symptoms and new view on life.

As discussed in chapter two several COS developers have included qualitative explorations to gain a better understanding of the outcome domains the most important to patients. However, a number of these studies are limited by the transparency of their reporting (Potter et al., 2015a, Wylde et al., 2014), despite a clear rationale for these explorations to gain a view from all key stakeholders there is limited evidence of the reported benefits of such explorations. This is one of the few studies indicating the benefits of qualitative explorations to understand and identify outcomes of important to patients, for consideration for inclusion as part of a core outcome set.

Strengths and limitations

A major strength of this study is the depth of understanding of the individuals lived experience of surviving a cardiac arrest through an Interpretative Phenomenological approach to analysis. IPA is idiographic focussing on the

experience of the individual, this was particularly important to understanding the lived experience of surviving a cardiac arrest, which is a personal, unexpected experience that can vary greatly between individuals.

These study findings are strengthened by the inclusion of interviews with three patients' partners. These interviews supported the accounts of patient participants and identified additional aspects of emotional well-being that were not highlighted in patient interviews. These included a loss of confidence and changes in personality. Patient's partners were willing to be interviewed and interested in the study as this has also had a large impact on their life, which was identified in both patient and partner interviews.

This study experienced challenges with recruitment due to the low survival rates of cardiac arrest. Further to this it was not possible to capture the views of those that had more severe cognitive impairment. Attempts were made to recruit partners from this population to provide an interview on their behalf this was unsuccessful. Earlier and regular contact to build a relationship with the family members during visiting times may have benefited this approach (Dicicco-Bloom and Crabtree, 2006). Different approaches to recruitment including wider cardiac rehabilitation classes or support networks through organisations such as the British Heart Foundation may have aided recruitment.

Implications of findings

The findings of this research highlight the areas of health that are the most important to cardiac arrest survivors. These outcome domains provide a conceptual framework to inform the development of a core outcome set.

This information from the patients' perspective brings to our attention the areas that have had an impact on patients' lives, giving additional insight for future research targets and health assessment that is useful and important to survivors. In addition to this the findings of this research could help inform documentation for cardiac arrest survivors, helping them to prepare for some of the symptoms they may be faced with in their recovery with many survivors unsure what to expect.

Through gaining a better understanding of what it is like to survive and recover from a cardiac arrest, the health outcomes that are the most important to patients have been identified. Many of these outcomes are not currently reported in randomised controlled trials, the highest basis of evidence that helps inform the care provided to individuals. This contribution is key to development of a core outcome set in this field to ensure that outcomes of importance and relevant to patients are considered.

Chapter 5: Consensus

development on the most

important outcome domains: An

International, multiple-perspective

modified Delphi Survey

5.1. Introduction

This chapter brings together the findings of chapter 3 and 4 to begin consensus development on the most important outcomes to cardiac arrest effectiveness trials. Different methods for developing consensus were explored in detail in chapter 2. As a consequence, a two-stage process in developing consensus on the core domain set for cardiac arrest clinical trials was selected. This chapter will describe the first step, an international modified Delphi Survey.

Section 4.2 describes the steps taken in survey development and survey conduct. Section 4.3 describes the results of rating and ranking exercises from different stakeholder groups completing the modified Delphi survey. The chapter will conclude with a summary of the findings, the strengths and limitations, informing the next stage of consensus development.

Aims:

To identify the outcome domains judged as most important for inclusion in a core domain set for cardiac arrest effectiveness trials, as determined by a range of international stakeholders: healthcare professionals, researchers, patients and their partners.

5.2. Methods

5.2.1. Survey development

Four key stages are described: 1) Question generation and adoption of an outcome framework; 2) Selection of an appropriate response scales; 3) Question structure; 4) Piloting of the questionnaire; and 5) The definitions of consensus. Two separate surveys were run in parallel for 1) healthcare professionals and researchers and 2) patients and partners', to explore the differences in view between stakeholder groups and ensure understanding. Considerations and challenges in questionnaire development will be discussed.

5.2.1.1. Question generation and adoption of an outcomes framework

The outcome framework for the modified Delphi survey development occurred with the: identification of outcome domains, application to a classification framework and adaption in response to piloting and steering group comments. The final framework is presented in Appendix 5.2.

Identifying outcome domains

Generation of the list of outcome domains included in the Delphi survey questionnaire was informed by the review of current outcome reporting in cardiac arrest randomised controlled trials (chapter 3) and interviews with cardiac arrest survivors and their partners' (chapter 4). The systematic review identified 164 outcomes across the three domains of the ICF classification: body structure and function, survival, and activities; and the

additional domains: survival and processes of CPR. Although a large number of outcomes were identified, this number represented the assessment of outcomes from the same outcome domain with differences in measurement tools, terminology, definitions and time point of assessment. Therefore, outcomes were regrouped and classified into outcome domains within a framework, reducing repetition and readability of the survey.

Further developing the outcome framework, five subordinate themes were identified from interviews with survivors of cardiac arrest and their partners. The five themes contributing to a disruption to normality were: survival; physical function; emotional well-being; social well-being and participation; and the impact to others. Newly identified themes including emotional well-being; social well-being and participation; the impact to others and subdomains within physical symptoms were introduced the outcome framework.

Each outcome was illustrated with examples informed by methods of assessment identified from the systematic review and/or patient quotes. No names of individual measurement tools were given as examples to ensure participants were voting on the importance of outcome domains rather than on the importance of specific measurement tools.

Application of a classification framework

As discussed in chapter 1, several outcome frameworks have been proposed which seek to assist with understanding the key components of outcome

assessment (WHO, 2001, Boers et al., 2014c, Wilson and Cleary, 1995). To assist with the classification of outcomes identified in the systematic review the ICF framework was applied and expanded. More recently OMERACT 2.0 filter has been developed to inform COS development; recommendations include the consideration of outcome domains across four core areas- death, life impact, economic impact/resource use and pathophysiological manifestations (Boers et al., 2014c, Idzerda et al., 2014).

When considered in light of the findings from the systematic review (chapter 3) and the qualitative interviews (chapter 4), the inclusion of survival as a core area, alongside life impact, pathophysiological manifestations and economic impact suggested a better fit with the needs of the COSCA study than was observed for the ICF framework. Therefore, the OMERACT 2.0 filter was adopted as a framework for the developing Delphi questionnaire, supporting the grouping of potential outcome domains across the four core areas.

Adaption to comments and piloting

In addition to the OMERACT framework application, the survey questions were listed across the time frame of the patient journey. Developing the framework was complex due to the reporting of outcome domains at a range of time points in particular survival. Survival at multiple time points in the patient journey is unique to life threatening health conditions such as cardiac arrest and therefore was included in the initial survey outcome framework.

After survey piloting detailed later in this section (5.2.1.4) the outcomes within the framework were listed across the appropriate time points as judged by the steering committee across: during CPR, immediately after CPR, during hospital stay, at hospital discharge and within the first year.

Outcomes were reclassified by steering group members to produce an outcome framework understandable for participants. One change from the systematic review was that outcomes classified fluid regulation was better described as renal function. Outcome assessment in cardiac arrest is complex, with a wide range of measurement tools used to assess neurological outcome and functional status. As a result, brain function was described across the patient journey with examples describing both biochemical markers of brain function and scale assessment qualities of neurological outcome. Measurement tools reported in the review (Cerebral Performance Category, modified Rankin Scale and Barthel Index) were explored to inform examples for both brain function or activities of daily living. This was further developed by examples of cognitive impairment described in interviews.

A small number of outcome domains that were identified from the systematic review were not taken forward for consideration in the Delphi survey, these outcomes were classified as 'process measures.' The reason for their exclusion from the Delphi survey was their relevance to specific intervention (e.g. the effectiveness of cooling devices) which would have little value to all cardiac arrest trials. Other outcomes within the classification of 'processes of

care' were considered as indicators the system and care provided e.g. CPR quality, and were part of study reporting but not measurable outcomes.

5.2.1.2. Response scale

Various response options have previously been applied to support participants in Delphi surveys to indicate the most important outcome domains. Commonly in COS development participants are asked to rate listed outcome domains on their importance (Devane et al., 2007, Sinha et al., 2012, Harman et al., 2015, Schmitt et al., 2011, Taylor et al., 2008) or rank the listed outcome domains for their relative importance (Mease et al., 2008, Bartlett et al., 2015). Alternative approaches include: listing a set number of the most important outcome domains (Ruperto et al., 2003), distributing points between a list of outcomes to indicate relative importance (Taylor, 2005, Mease et al., 2008) and voting yes or no for CDS inclusion (Bartlett et al., 2012, Moza et al., 2015).

There are a number of considerations when selecting response options, each requiring different levels of cognition, consideration and time for completion. Minimizing cognitive requirements and time required for completion would help assist both patient and healthcare professional participation. Rating and ranking exercises require less cognitive attention and time than approaches such as the distribution of points which may be challenging for participants (Streiner et al., 2014). Voting yes or no for CDS inclusion of outcome domains may be a challenging question for participants

in early stages of consensus development and would not allow participants to indicate discrimination of importance between outcome domains.

Rating or ranking items were considered to be the most appropriate question types for the nature of this research. These types of questions ensure participants consider all listed outcome domains, this was important due to the efforts made to identify outcome domains (chapter 3: systematic review and chapter 4: interviews with patients and their partners).

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) scale has been widely applied in completed (Douglas et al., 2009, Harman et al., 2013, Khanna et al., 2008, Schmitt et al., 2011, Waters et al., 2014, Saketkoo et al., 2014b, McCann et al., 2015) and planned modified Delphi surveys for CDS development (MacLennan et al., 2015, McCann et al., 2015, Keeley et al., 2015). The GRADE scale was originally recommended to help provide recommendations for the framing of questions when deciding on important outcomes in the context of evaluating treatment recommendations (Guyatt et al., 2011). The scale adopts a nine-point numerical scale with textual descriptions where 1-3 limited importance, 4-6 important and 7-9 critical to decision making (Figure 5.1).

Figure 5.1: Examples of the GRADE Scale (Example from the healthcare profesional and researcher survey).

* 11. **Renal function** immediately after CPR. *For example: the need for dialysis, kidney function tests or urine output.*

Limited importance		Important					Critical	
1	2	3	4	5	6	7	8	9
<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

* 12. **Survival** immediately after CPR. *For example: sustained ROSC, 4 hour survival or 24 hour survival.*

Limited importance		Important					Critical	
1	2	3	4	5	6	7	8	9
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>

Several COS development modified Delphi surveys have used shorter, five point scales (Devane et al., 2007, Distler et al., 2008, Sinha et al., 2012, Smaïl-Faugeron et al., 2013, Karas et al., 2014). However some of these studies have resulted in more than 30 outcome domains reaching consensus and included as part of a core outcome set (Devane et al., 2007, Karas et al., 2014). A scale with too many steps may affect the cognitive requirement of participants, with a report suggesting that scales with nine steps and greater can cause cognitive overloading for participants (Hawthorne et al., 2006). However, a larger nine point scale may be advantageous over the five point

scale as this would further support the discrimination of importance and reduce the risk of end aversion bias (Streiner et al., 2014).

COSCA Delphi survey questionnaire

For the purpose of the COSCA study, the 9-point GRADE scale was selected to facilitate participants in rating each outcome domain for importance to their clinical decision making or important to them as cardiac arrest survivors.

However, due to the high level of consensus on the critical importance of a large number of outcomes included in round 1 of the survey and the failure to achieve sufficient discrimination between outcomes, an alternative response scale was adopted for round 2. Healthcare professional and researchers were invited to rank the top 10 most important outcomes domains after the removal of outcomes reaching consensus of critical importance in round 1. Patient and partners survey were asked to rank their top 5 remaining outcome domains reflecting a shorter list of outcome domains presented.

5.2.1.3. Question structure

Good practice guidance in questionnaire formatting requires that instructions to participants are clearly visible and easy to read (McColl et al., 2001). The first round of the modified Delphi survey began with an introduction including the aims of the research and what to expect from the survey. It was explained that there would be at least two rounds of surveys with the opportunity to respond to group results in subsequent rounds. Survey introductions were different in terminology and content between stakeholder

groups to ensure understanding and readability. One difference was that the classification framework applied was described in the healthcare professional researcher stakeholder group to provide sufficient context. This was excluded from the patient and partner survey to avoid overloading with information that may not prove useful. To aid readability the SMOG (Simple Measure of Gobbledegook) score (Laughlin, 1969) was applied, this is a score that considers the complexity of sentence structure. High scoring sentences were adapted to reduce sentence complexity.

Clear instructions were provided at the top of each survey page: first, the core area to be considered was highlighted; second, a summary description of the outcome domains listed was provided; finally, the scoring system was illustrated. In round 1 each page contained up to 7 outcome domains each was supported by an agreed definition and example; the GRADE scale and was presented below each question. Round 1 of the survey also provided participants with the opportunity to list any additional outcomes they thought were important and missing from the list.

A similar structure was taken in round 2, with information explaining changes and what to expect in this round of the survey. In both surveys the ranking exercise appeared on a single page in order to view all considered outcome domains considered in the ranking at the same time point.

5.2.1.4. Piloting

The questionnaire was assessed for readability, comprehension, clarity and content with: the steering group members; a group of health professional and researchers; and with patients with a range of medical histories from the Clinical Research Ambassador Group (CRAG), representing the views of stakeholders participating in the survey. Piloting steps and findings are described below.

Pilot evaluation with patient partners

Following a group discussion during which the purpose of the Delphi survey was explained, patient partners from the Clinical Research Ambassador Group (CRAG) were invited to self-complete the survey either as a pen and paper questionnaire (n=2) or online (n=3), without the assistance of the researcher at their own convenience. Along with the survey a short questionnaire asked about the content and length of the survey were included to obtain feedback. Patient partners who completed the paper-based version were asked to return the questionnaire in a reply-paid envelope.

From the options referring to the length of the survey: 'far too short', 'a little bit too short', 'just right', 'a little bit too long' and 'far too long', all patient partners scored the survey as just the right length. Questionnaires asked participants if they had any general comments about the survey, if there was any content missing and if there were any sections of the survey that were difficult to understand. One comment highlighted that the instructions for

partners' completing the survey was not clear enough and this section was modified to increase transparency reflecting this comment. After initial online and postal survey completion and feedback, a subsequent face to face meeting was held with a patient partner from CRAG who had survived an in-hospital cardiac arrest and their partner.

In the discussion the patient partner explained how it was difficult to compare the importance of pathophysiological measures such as the functioning of organs and things that contribute to his daily life as they had varying importance at different time points. He described how some outcome domains listed were more important during his hospital stay and others that would have been more important once he returned home.

Pilot evaluation with healthcare professionals

A face to face discussion took place with a multi-disciplinary team of clinical researchers (n=5) that conduct trials with cardiac arrest participants, to review the survey contents and structure. The group found it difficult to score the importance based on the current format of the survey with outcome domains grouped by core area, raising the that the time point of measurement influenced the importance of the outcome domain and how they would score in the survey. The healthcare professionals explained how different outcomes would have a different meaning across the time point of assessment. At this meeting the potential different measurement time points were discussed, healthcare professionals highlighted five distinct time points relevant to the patient journey and outcome domains that are currently

reported across trials. These were: during CPR; immediately after CPR; during hospital stay; at hospital discharge; and within the first year of surviving a cardiac arrest.

In addition to this email communication occurred with steering group members', changes in response to comments are described earlier in section 5.2.1. This was reviewed by three different nationalities to ensure there was translational understanding of the terms used in the survey.

Responses to survey piloting

In response to piloting the survey a number of changes were made to the modified Delphi survey to incorporate issues raised. An important issue raised by both stakeholder groups that influence the survey content and structure was the importance of outcome domains at different stages of the patient journey. Grouping outcome domains by time point raised a number of challenges and resulted in differences between the two surveys for different stakeholder groups.

Patients' recall and understanding of different time points may limit their ability to make judgments on the importance of outcome domains listed specific time points included in this survey. For this reason, patients were not questioned on the importance of outcomes during CPR and immediately after CPR. A logic question was included in the patient and partner survey tailoring the questions of the survey to their recall of their time during hospital

stay and therefore their ability to make a judgment of outcomes importance at this time point.

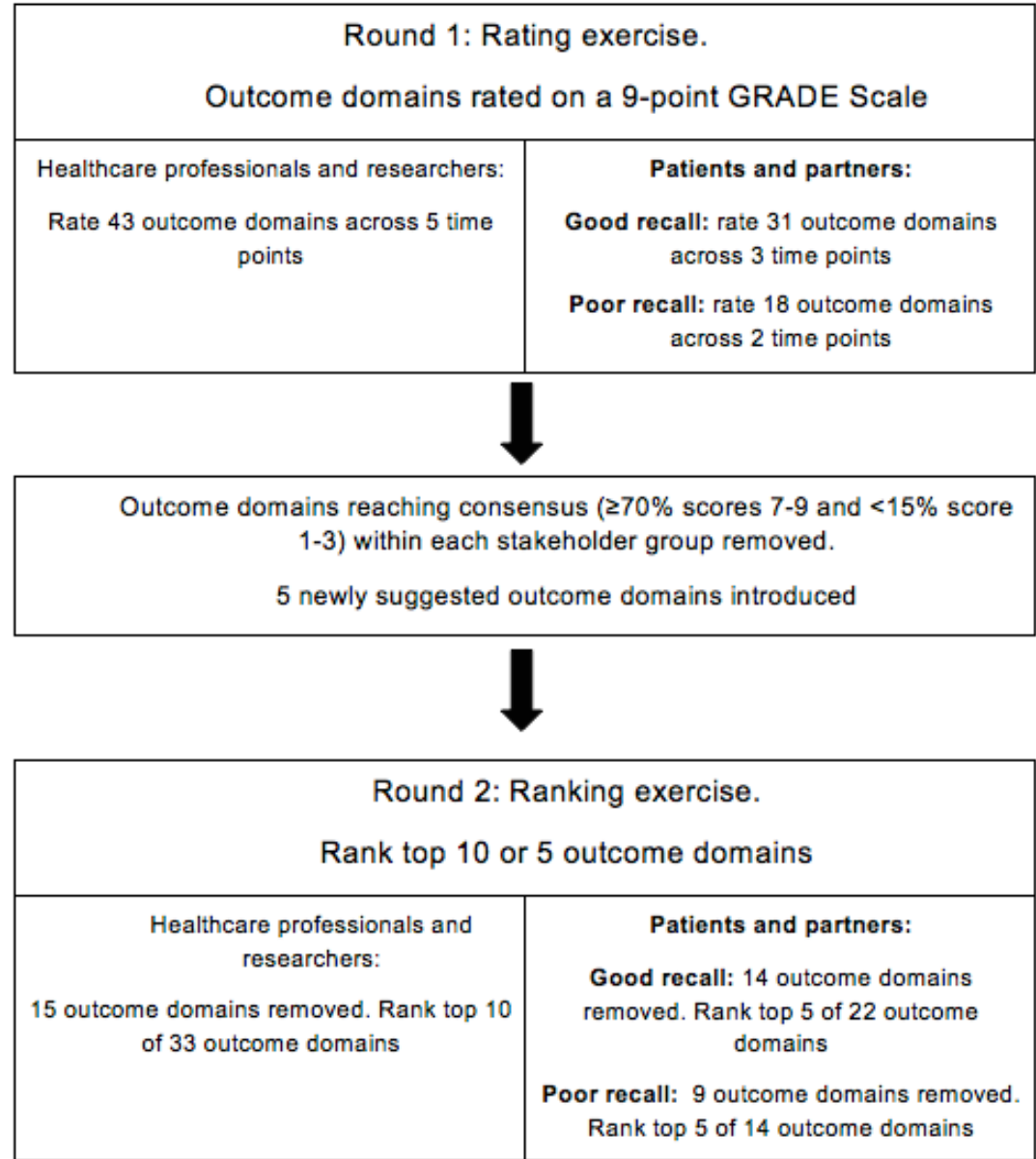
Importance of outcome domains at different time points significantly increased the length of the survey (from 21 to 43 in round 1). As the patient and partner group were only questioned about the importance of outcomes at a maximum of three time points, it was possible to group the outcome domains at multiple time points in one place reducing repetition and confusion. This format was explored for the healthcare professional and researcher survey, but raised visual formatting issues with outcome domains being considered at five time points (figure 5.2). In the healthcare professional and researcher survey each page focused on outcome domains at different time points. The final survey structure is summarised in figure 5.3.

Figure 5.2: Grade scale at multiple time points in the patient and partner survey.

9. **Activities of daily living.** For example being able to dress yourself, walking without support, washing and housework.

	Limited importance			Important				Critical	
	1	2	3	4	5	6	7	8	9
During hospital stay	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
At hospital discharge	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Within the 1st year	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>

Figure 5.3: Overview of the modified Delphi survey



5.2.2. Participants

Stakeholder representation

Good practice guidance (explored in Chapter 2) highlights the importance of including representative stakeholders throughout the process of CDS development. Despite the importance of the patient voice in COS identified in 2002, modified Delphi processes have historically involved clinical, academic stakeholders and industry representatives only (Ruperto et al., 2003, McGrath et al., 2008, Khanna et al., 2008, Taylor et al., 2008).

More recently groups have sought the views of patient stakeholders as participants in modified Delphi methods for CDS development (Wylde et al., 2014, Bartlett et al., 2012, Mease et al., 2008, Potter et al., 2015a). It is anticipated that the COSCA will be applied in future national and international cardiac arrest effectiveness trials: therefore, the target population for survey participation included clinicians and healthcare professionals (including nurses, doctors and allied health professionals (including paramedics)), directly involved in the care of cardiac arrest patients, clinical trialists and health researchers involved in cardiac arrest/resuscitation research, cardiac arrest survivors and the partners of survivors.

Historically, the voice of the survivors of cardiac arrest has not been clearly articulated. Whilst not yet explored in cardiac arrest, growing evidence of the discrepancies that exist in the outcomes judged to be important between clinicians and patients (Kirwan et al., 2003, Saketkoo et al., 2014a).

Inclusion and exclusion criteria

Eligibility criteria for participation in the modified Delphi survey was defined as follows:

- *Healthcare professionals* currently involved in the provision of care for cardiac arrest patients, intensivists, paramedics, emergency physicians, cardiologists nurses and rehabilitation specialists.
- *Academics* with experience in the field of cardiac arrest research.
- *Adult survivors of cardiac arrest* who had not sustained cognitive impairment as a consequence of the arrest, and hence were able to complete the survey with the capacity to self-consent. Discharged from hospital for at least 3 months prior to survey completion.
- *Partners of the survivors* of cardiac arrest
- Over the age of 18
- Sufficient understanding of the English language

Sample size

Traditionally Delphi panels have comprised of under 50 participants with many involving between 15 and 20 participants (Hsu and Sandford, 2007b). The advent of modifications to the Delphi process has resulted in wide ranging numbers of participants: from the field of COS development, these numbers have ranged from fewer than 50 (McGrath et al., 2008, Taylor et al., 2008, Schmitt et al., 2011) to more than 200 in round one of a multi-round survey (Bartlett et al., 2012, Saketkoo et al., 2014b, Devane et al., 2007). One modified Delphi study in CDS development for breast reconstruction survey reporting more than 300 participants in round 1 (Potter et al., 2015a).

However, there is a lack of consensus or recommendation on the number of participants in modified Delphi surveys (Sinha et al., 2011).

Recent studies have reported round 1 modified Delphi survey participant numbers between ranges of 80-150 in COS development including in the health areas including: asthma (n=95) (Sinha et al., 2012); *fibromyalgia* (n=96) (Mease et al., 2008); *acute diarrhoea* (n=101) (Karas et al., 2014) and *cleft palate* (n=146) (Harman et al., 2015). After considering previously completed Delphi surveys in the field of CDS development a target sample of 150 for round 1 was set. This number was balanced between the number of participants completing previous Delphi studies in COS development; allowing for a range of stakeholder views, some participant drop out between rounds and a manageable data set.

Recruitment

A snowballing approach was taken for recruitment to the modified Delphi survey. Snowballing describes when people or organisations participating in research are asked to suggest other research participants (Griffiths, 2009). This approach is particular useful for the recruitment of hard to reach groups and identifying large convenience samples through networks (Wagner and Lee, 2014).

Snowballing sampling was taken via International Liaison Committee On Resuscitation (ILCOR) networks. ILCOR have 27 taskforce members and each were asked to invite 6 healthcare professional and 3 patients to

participate in the relevant surveys using email invitation templates and information attachments about the study. This snowballing technique highlighted contacts with the Australian and Korean resuscitation committees and patient advocacy groups (Sudden Cardiac Arrest Foundation).

Potential participants were invited by email with a link directing them to the survey. In round one participants were asked to enter their email address in order to receive links to subsequent survey rounds with individualised feedback. Participants were also provided with a study contact point if they had any questions about the survey. Email addresses were assigned a personal ID that corresponded to individualised feedback pdf.

Ethical considerations

Ethical approval was granted by NRES (National Research Ethics Service) Committee West Midlands-The Black Country after meeting the approval conditions resulting from the REC (Research Ethics Committee meeting) (REC number 13/WM/0464) of this study. Invitation letters are included in appendix 5.1.

5.2.3. Modified Delphi survey process

This section described the steps in survey procedures including survey administration, data collection and data analysis.

Survey administration and data collection

The survey was conducted using the online software platform SurveyMonkey Inc (Palo Alto, California, USA). The platform provided the benefits an unlimited number of responses, data set extraction and an easy to use platform for the style of survey questions.

The Delphi survey ran between March and June 2015. Round 1 was open for 4 weeks to allow for snowballing with participants being advised that the survey would close upon 2 weeks of receiving the email. Round 2 of the survey was open for 3 weeks to allow for sufficient completion. Reminder emails were sent in round 2: 2 weeks, 1 week and 1 day before the survey closed.

Round 1 of the survey invited participants to rate outcome domains, the survey did not allow participants to progress unless all questions had been answered but ticking a box per question. Demographic details were obtained in round 1 of the survey including: age, gender, nationality and role in cardiac arrest research or care. Participants were asked to enter their email at the end of the survey in order to receive the next round of the survey. In round 2 it was not possible to restrict the number of items participants ranked from a drop down menu. It was possible for participants to use numbers more than

once but participants were clearly instructed to rank outcome domains 1-5 or 1-10 and to leave the remainder of outcome domains unscored (Figure 5.4).

Figure 5.4: Round 2 ranking example from the patient and partner survey

4. At hospital discharge

	Number
Fatigue e.g. increased tiredness, feelings of exhaustion or tiredness from doing nothing.	<input type="text"/>
Emotional well-being e.g. feeling of anxiety, feeling down, reduced confidence or post-traumatic stress disorder.	<input type="text"/>
Participation e.g. being able to complete normal working or voluntary roles, carer roles, being able to do the same leisure activities (including sports) and being able to socialise like before.	<input type="text"/>
Health related quality of life e.g. the assessment of a patients' overall well-being that may have been impacted by a cardiac arrest, that is physical, social and emotional well-being.	<input type="text"/>
Family impact e.g stress and anxiety and added pressure to relationships.	<input type="text"/>
Discharge location (<i>New outcome</i>) e.g. discharge to home or nursing facility	<input type="text"/>

5. Within the first year

	Number
Fatigue e.g. increased tiredness, feelings of exhaustion or tiredness from doing nothing.	<input type="text"/>
Emotional well-being e.g. feeling of anxiety, feeling down, reduced confidence or post-traumatic stress disorder.	<input type="text"/>
Participation e.g. being able to complete normal working or voluntary roles, carer roles, being able to do the same leisure activities.	<input type="text"/>
Family impact e.g stress and anxiety and added pressure to relationships.	<input type="text"/>
Complications e.g. side effects of medication or ICDs complications.	<input type="text"/>
The economic cost to an individual (<i>New outcome</i>) e.g. the cost of absence from employment, additional transport or increased care.	<input type="text"/>

Data were extracted from SurveyMonkey and managed in Microsoft Excel with corresponding personal IDs. Email addresses were managed with corresponding personal IDs separately to results to anonymise individual participants scores from the research team.

Data analysis

In round 1 where participants had started the survey, but failed to respond to >75% of the outcome rating scores their scores were removed to allow for suitable comparison of score of outcome domains listed across the Delphi survey. For each question (up to 43 outcome domains in round 1) *group mean, median and range were calculated. Percentages of score distribution across the sub-sections of the GRADE scale were calculated to determine whether predefined consensus of critical or limited importance has been achieved.*

The change from a rating to ranking exercise in round 2 required a change to analysis. Ranking exercises have rarely been used in COS development and have not been transparently reported (Bartlett et al., 2012, Ruperto et al., 2003, Mease et al., 2008). *First a points system considering the relative rank of outcome domains was considered. However, this was complex due to the differences in healthcare professional and researcher survey to patient and partner surveys with a different number of outcome domains at different time points between surveys. In addition to this, with the inclusion of completion errors in the patient and partner group and different numbers of outcome domains within this group due to recall this was not a suitable approach. As a result, outcome domains were ranked in order on the percentage of*

participants including the outcome domain in their ranking of top 5 or 10, and consensus values were set.

Consensus definition

In round one, the consensus definition of critical importance for outcome domains was informed by earlier COS development studies (Harman et al., 2013, Devane et al., 2007, Boers et al., 2015) and defined a priori as $\geq 70\%$ of participants selecting a score between 7-9 ('critical importance') and $< 15\%$ of participants selecting a score of between 1-3 ('limited importance'). The consensus definition of limited importance was predefined as $\geq 70\%$ selecting a score of between 1-3 ('limited importance') and $< 15\%$ selecting a score of between 7-9 ('critical importance'). Due to the large number of outcome domains included in the survey, any reaching consensus of critical or limited importance during round one were removed and not considered further during round 2.

Due to the decision to revise the response option for round two (to a ranking of outcomes in order of importance), a revised approach to determining consensus in round 2 was adopted. Outcome domains that were ranked as the most important (top 10 for clinicians and top 5 for patients) by $\geq 70\%$ of participants were judged to have reached consensus of critical importance. This process did not take into consideration the relative ranking of domains.

This approach took into consideration the large number of outcome domains that would be unranked: items that were given a rank of importance by fewer

than 15% of participants were judged to be of limited importance. For outcome domains where $\geq 60\%$ of participants provided a ranking of importance (but the higher level of 70% was not achieved), a decision to consider these further during the planned consensus meeting was made with the indication these outcome domains had reached lower levels of consensus.

Feedback

With the invitation to participate in round 2 of the survey, all participants received feedback scores from round 1. The software did not support the generation of an individual summary in comparison to group data; therefore, all data was extracted manually. Alongside the email invitation, changes to the survey were described and a feedback pdf file was attached (Appendix 5.3). The feedback pdf explained that outcome domains reaching consensus had been removed and the addition of newly suggested outcome domains. Participants received a copy of their scores from round 1 where consensus was not achieved, alongside the group median score. The GRADE scale in round 1 was reiterated and that participants would rank outcomes domains next with 1 indicating the most important, highlighting this difference from round 1.

Feedback of results were anonymous to the group. Participants were assigned a personal ID this was the only part of the feedback sheet that was identifiable to the researcher to allow email correspondence for invitations

and reminders. Each participant received feedback from their participant group only.

5.3. Results

5.3.1. Round 1 demographic results

Healthcare professionals and researchers

From a total of 113 healthcare professionals or researchers who started the survey, 99 (88%) completed the survey. The 14 participants who did not complete the survey, completed less than 75% of the items and hence were excluded from the group results. The decision to recruit participants via a snowballing approach meant that it was not possible to be certain of the total number of potential participants who were contacted; the lack of 'denominator' value prevented the calculation of a response rate for round 1.

Representatives from 14 countries completed the survey, from continents including Europe, North America, South America, Australasia and Asia (Table 5.2). The group included: physicians (48.4%), allied health professionals (21.1%), nurses (12.6%), academics (6.3%) and other (not further defined) (11.6%).

Patients and partners

From a total of 86 patients or partners starting the survey, 69 (80%) completed the survey. The 23 participants who did not complete the survey, completed less than 75% of the items and hence were excluded from the group results. The large majority of survey participants were survivors of cardiac arrest (89.6%). More than half of the patients (53.6%) had a limited recall of their time in the hospital following their arrest (Table 5.3).

Patient and partner participants represented 7 different countries (South Korea, Qatar, UK, Sweden, Australia, USA and Canada), the majority of participants were from the USA (78%) (Table 5.4). Participants were from a wide range of age categories across a lower range of 25-34 years up to 65-74 years. The most frequently represented age groups were 55-64 years (39.7%) and 45-54 years (26.5%) (Table 5.1). Most sustained their arrest more than one year before the survey (72%) the remaining participants were partners of those who had survived an arrest.

Table 5.1: Age and gender of round 1 participants

Age (years)	Healthcare professionals and researchers (n=96*)	Cardiac arrest survivors and partners (n=68*)
18-24	0	0
25-34	17% (16)	10% (7)
35-44	42% (40)	6% (4)
45-54	29% (28)	27% (18)
55-64	10% (10)	40% (27)
65-74	2% (2)	13% (9)
75 and over	0	4% (3)
Gender	(n =97*)	(n=67*)
Female	39% (38)	46% (31)
Male	61% (59)	55% (36)

Footnote: *There were 99 and 69 participants in each group but some participants chose not to disclose their gender.

Table 5.2: Nationality of Healthcare professional and researcher round 1 participants

Country n= 14	n=98*	Continent	% representation (n)
Korea	21	Asia	34% (33)
Qatar	12		
UK	8	Europe	21% (21)
Denmark	1		
Norway	3		
Serbia	1		
Finland	1		
Belgium	5		
Sweden	1		
Switzerland	1		
Australia	29	Australia	30% (29)
USA	11	North America	14% (14)
Mexico	2		
Peru	1	South America	1% (1)

Footnote: *1 participant did not disclose their nationality

Table 5.3: Level of recall of time in hospital in the patient and partner groups

Group	Recall of time in hospital	N=69
Group B: Good recall (45.6%)	The majority of it	18 (26.1%)
	Quite a bit	14 (20.3%)
Group C: Poor recall (54.4%)	A fair bit but mainly based on what others have told me	16 (23.2%)
	Only a bit	17 (24.6%)
	Nothing	4 (5.8%)

Table 5.4: Time since arrest of patient and partner participants:

Time since arrest	N (65)
3-6 months	13.8% (9)
7-12 months	13.8% (9)
>12 months	72.4% (47)

Table 5.5: Nationality of patient and partner round 1 participants:

Country (n= 7)	n=68	Continent	% representation (n)
South Korea	1 (1.5%)	Asia	3% (20)
Qatar	1 (1.5%)		
UK	6 (8.8%)	Europe	9% (6)
Sweden	1 (1.5%)		
Australia	3 (4.4%)	Australia	4% (3)
USA	53 (77.9%)	North America	82% (56)
Canada	3 (4.4%)		

5.3.2. Round 1 survey results: rating the importance of outcome domains

Healthcare professionals and researchers

From the total number of 43 outcome domains (from 13 health domains at multiple time points) listed for health professionals in the round 1 survey, 15 outcome domains (from 11 health domains at multiple time points) reached the high pre-defined level of consensus (Table 5.5): $\geq 70\%$ of participants score between 7-9 (of critical importance) and $<15\%$ scored between 1-3 (limited importance). No outcome domains reached consensus of limited importance ($\geq 70\%$ scored between 1-3 (limited importance) and $<15\%$ scored between: 7-9 (critical importance)).

The core area survival, was judged to be of critical importance, reaching the high level of consensus, at all five time-points in the patient journey. Three outcome domains listed within the core area pathophysiological manifestations also reached consensus across two time-points: circulatory function immediately after CPR; circulatory function during hospital stay; and brain function during hospital stay.

Seven outcome domains listed within the core area of life impact reached consensus – three assessed at hospital discharge, and the remaining four within the first year of the event: brain function at hospital discharge; physical symptoms at hospital discharge; activities of daily living (ADL) at hospital discharge; brain function within 1 year; physical symptoms within 1 year; ADL within 1 year; and health related quality of life (HRQoL) within 1 year.

Outcome domains that did not reach consensus of critical importance within the pathophysiological manifestations core area included: renal function, respiratory function and adverse events. Those not reaching consensus within life impact included fatigue, emotional well-being, participation and family impact.

Patients and partners

From the total number of 32 outcome domains (13 health domains at multiple time points) listed for patients and partners in the round 1 survey, 14 (10 health domains at multiple time points) reached the high pre-defined level of

consensus (Table 5.6): $\geq 70\%$ of participants score between 7-9 (of critical importance) and $\geq 15\%$ scored between 1-3 (limited importance). No outcome domains reached consensus of limited importance ($\geq 70\%$ scored between 1-3 (limited importance)) and $\leq 15\%$ scored between 7-9 (critical importance).

The outcome area, survival, was judged to be of critical importance, reaching the high level of consensus, at all time-points in the patient journey. Three outcome domains listed from the core area pathophysiological manifestations reached consensus: circulatory function during hospital stay, respiratory function during hospital stay and adverse events within a year. Six outcome domains, all at the time point within 1 year reached consensus: health related quality of life; emotional well-being, family impact; participation; physical symptoms and fatigue.

All participant groups

From a total of 32 outcome domains that were common to both groups, eight reached consensus in each both groups –survival during hospital stay; circulatory function during hospital stay; survival at hospital discharge; survival within 1 year; brain function within 1 year; physical symptoms within 1 year; activities of daily living within 1 year; and HRQoL within 1 year.

Three outcome domains reaching consensus in the healthcare professional and researcher group in round 1 were not included in the patient and partner survey due to patient recall at this time point. From common outcome domains, four reached consensus of critical importance in the healthcare

professional and researcher group only - one during hospital stay and three at discharge: brain function during hospital stay; physical symptoms at hospital discharge, brain function at hospital discharge and ADL at hospital discharge. From common outcome domains, five reached consensus of critical importance in the patient group only – one during hospital stay and the remaining four within one year: respiratory function during hospital stay; fatigue within 1 year; emotional well-being within 1 year; participation within 1 year; family impact within 1 year and side-effects within 1 year.

There was no single outcome domain which was judged to be of critical importance by all participants; the highest scoring domains were brain function at hospital discharge in the healthcare professional and researcher group (93% judged this to be of critical importance) and circulatory function during hospital stay in the patient and partner group (91%). All round 1 scores across participant groups are detailed in appendix 5.4.

Participant comments and suggested outcome domains

Participants in round one listed five additional outcome domains that were judged not to be included in the initial survey: discharge location; cost effectiveness of an intervention; the economic impact to an individual; the duration of stay in intensive care; and the duration of hospital stay. Other comments contributed to examples for examples provided for outcome domains, for example post-traumatic stress disorder was added to emotional wellbeing.

All suggestions were classified under the core area 'economic impact and resource use' and included in the revised round 2 survey. Several process measures such as time to defibrillation and CPR quality were also suggested. However, these are not judged to be measures of the outcome but measures of care provided and hence were not considered further.

Table 5.6: Outcome domains reaching consensus in round 1: Healthcare professional and researcher participants. In order of highest level of consensus of critical importance.

Rank order	Outcome domain (% scores 7-9 (critical importance))
1.	Brain function at hospital discharge (93%)
2.	Survival at hospital discharge (92%)
3.	Brain function within 1 year (89%)
4.	Survival within 1 year (89%)
5.	Brain function during hospital stay (87%)
6.	Survival during hospital stay (87%)
7.	Survival during CPR (86%)
8.	Circulatory function immediately after CPR (79%)
9.	Physical symptoms within 1 year (82%)
10.	Physical symptoms at hospital discharge (81%)
11.	Survival Immediately after CPR (78%)
12.	Activities of daily living within 1 year (77%)
13.	Health related quality of life within 1 year (75%)
14.	Activities of daily living at hospital discharge (73%)
15.	Circulatory function during hospital stay (70%)

Table 5.7: Outcome domains reaching consensus in round 1: patient and partner participants. In order of highest level of consensus of critical importance. The outcome domains listed in italics are from patients with higher recall only.

Rank order	Outcome domain (% scores 7-9 (critical importance))
1.	<i>Circulatory function during hospital stay (91%)</i>
2.	Survival within 1 year (90%)
3.	Health Related Quality of Life within a year (90%)
4.	Survival at hospital discharge (88%)
5.	Emotional Well-being within a year (86%)
6.	<i>Survival during hospital stay (84%)</i>
8.	Brain function within 1 year (83%)
8.	Family impact within a year (83%)
9.	Participation within 1 year (80%)
10.	Activities of daily living within a year (80%)
11.	<i>Respiratory function during hospital stay (79%)</i>
12.	Physical symptoms within 1 year (73%)
13.	Fatigue within 1 year (71%)
14.	Adverse events within 1 year (71%)

5.3.3. Round 2 completion

Healthcare professionals and researchers

From the total population of 99 Group A participants in round 1, e-mail invitations to participate in round 2 were successfully delivered to 96 (97 %). 3 participants were lost due to a lack of / or incorrect email address. Almost 60% of invitees (n=55/96; 57.3%) completed the second round survey (figure 5.5).

Unfortunately, 9/55 participants failed to complete the survey as instructed; this data was not usable. The most common error was scoring all outcome domains rather than providing a rank order of importance for the top ten outcome domains. Responses with completion errors were not included in the group results because it was not possible to interpret whether a score of 1 indicated the most important or least important due to changes in scoring approaches between rounds of survey. Participants who had failed to appropriately rank order the domains in order of importance were invited to complete the survey again; three agreed to do so, but only one recompleted without errors. A total of 47 (47/55; 85%) participants completed the ranking exercise correctly and their scores were included in the final analysis.

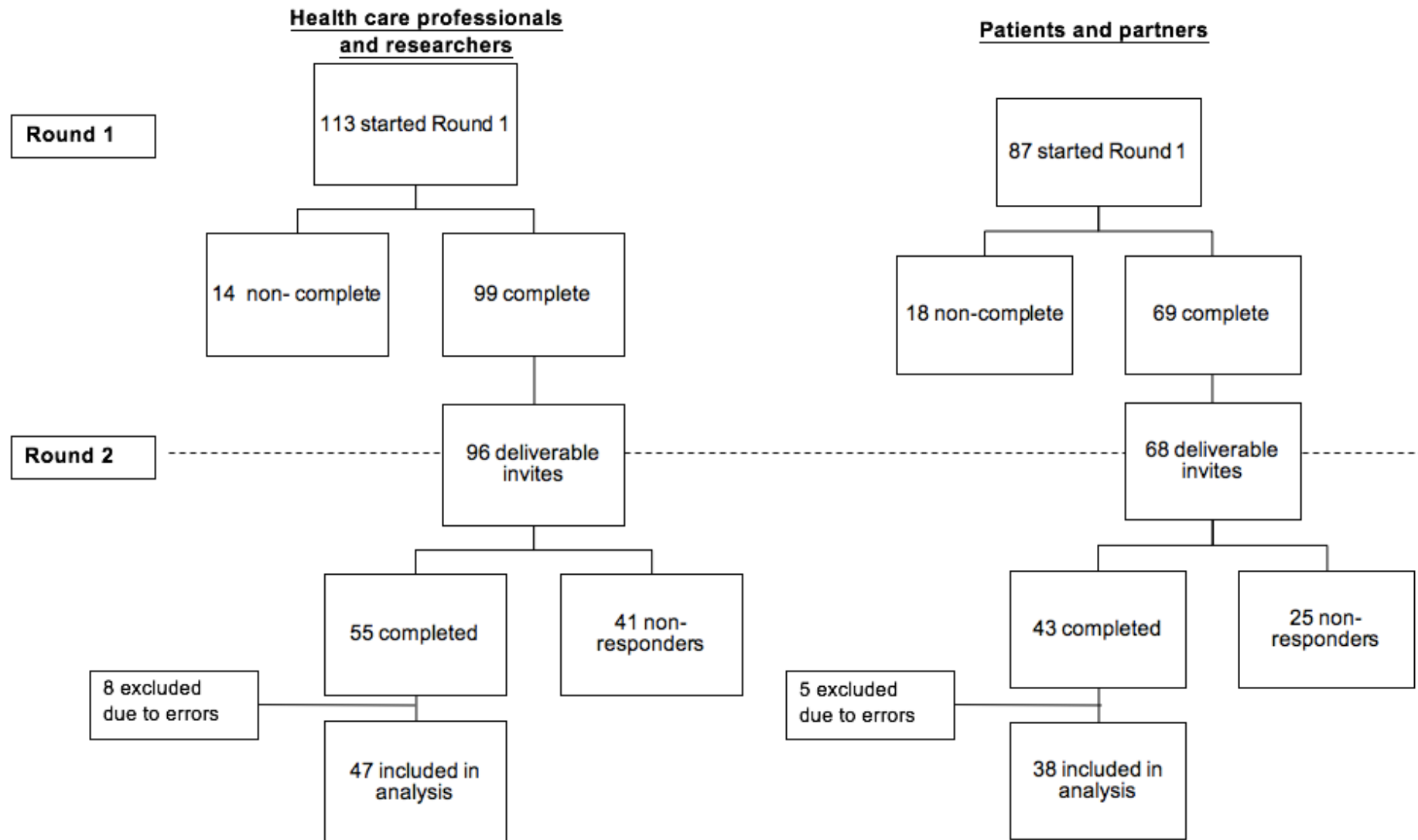
Patients and partners

From the total population of 69 Group B and C participants in round 1, e-mail invitations to participate in round 2 were successfully delivered to 68 (99%), with 1 participant from round 1 being lost due to an incorrect email address.

Over 60% of invitees (n=43/68; 63.2%) completed the second round survey (figure 5.5).

Similarly, to the healthcare professional and researcher group there were a number of completion errors in the second round of the survey. The majority of errors (n=7) were in the patients with good recall where the survey was separated by time point and participants ranked a top 5 for both sections. As it was to interpret the order of importance results were included in the analysis. 5 participants scored all outcome domains and responses were removed from the survey as it was possible to interpret whether a score of 1 indicated the most important or could indicate a GRADE scale score. 38 responses were included in the analysis of round 2 (n=38/68 55.9%).

Figure 5.5: Participants across stakeholder groups in round 1 and 2 of the modified Delphi survey.



5.3.4. Round 2 survey results: ranking the importance of outcome domains

Healthcare professionals and researchers

Consensus of critical importance in round two was set at >70% of participants including the outcome domain in their ranking, and limited importance <15% not including the outcome domain in their ranking. In round 2 the outcome domain, participation within 1 year reached consensus with 72.3% of round two participants including this in their top ten ranking (table 5.7). Three outcome domains - circulatory function during CPR (66%), brain function immediately after CPR (66%) and HRQoL at hospital discharge (62.7%) failed to achieve the high level of consensus – but were above a lower limit of 60%.

Eleven outcome domains reached consensus of limited importance with <15% of participants including the outcome domains in their top ten ranking. These were: renal function during CPR, renal function immediately after CPR, fatigue during hospital stay; fatigue at hospital discharge; fatigue within 1 year; adverse event during CPR; adverse events immediately after CPR; emotional wellbeing during hospital stay; emotional wellbeing at hospital; family impact during hospital stay and family impact at hospital discharge. Fatigue during hospital stay was the only item to not be ranked by any round two participants from this group.

Patients and partners

In round two both brain function (78.9%) and health related quality of life (76.3%) at hospital discharge reached consensus of critical importance with >70% of participants including these outcome domains in their top five ranking (or top ten in the case of completion errors) (Table 5.8). Brain function during hospital stay (68.8%) and participation at hospital discharge (60.5%) were close to consensus with >60% including in their ranking.

Seven outcome domains reached consensus of limited importance with <15% participants including in their ranking. These were: HRQoL during hospital stay; ADL during hospital stay; fatigue during hospital stay; cost effectiveness, discharge location; duration of stay in hospital and the duration of stay in intensive care. Further to this fatigue during hospital stay, duration of stay in hospital and the duration of stay in intensive care were all excluded from all participants' top five rankings (or ten ranking).

Table 5.8: Round Ranking results from the Healthcare professional and researcher group. In order of percentage of participants including outcome domain ranking 1-10.

Outcome	Time point	% including in ranking (1-10)
1. Participation	Within 1 year	72.3%
3. Circulatory function	During CPR	66%
3. Brain function	Immediately after CPR	66%
4. HRQOL	At hospital discharge	61.7%
6. Brain function	During CPR	46.8%
6. Discharge location	At hospital discharge	46.8%
9. Emotional well-being	Within 1 year	44.7%
9. Duration of stay in ICU	During hospital stay	44.7%
9. Participation	At hospital discharge	44.7%
11. Physical symptoms	During hospital stay	40.4%
11. Duration of stay in hospital	During hospital stay	40.4%
13. Respiratory function	immediately after CPR	36.2%
13. Health relate quality of life	During hospital stay	36.2%
15. Respiratory function	During CPR	31.9%
15. Activities of daily living	During hospital stay	31.9%
17. Respiratory function	During hospital stay	29.8%
17. Economic cost to an individual	Within 1 year	29.8%
18. Complications	Within 1 year	29.7%
19. Cost effectiveness	During hospital stay	25.5%
20. Renal function	During hospital stay	21.3%
22. Family impact	Within 1 year	19.1%
22. Adverse effects	During hospital stay	19.1%
24. Emotional well-being	At hospital discharge	14.9%
24. Adverse effects	Immediately after CPR	14.9%
26. Renal function	Immediately after CPR	12.8%
26. Fatigue	Within 1 year	12.8%
27. Family impact	At hospital discharge	10.6%
29. Emotional well-being	During hospital stay	8.5%
29. Family impact	During hospital stay	8.5%
30. Renal function	During CPR	6.4%
31. Adverse effects	During CPR	4.3%
32. Fatigue	At hospital discharge	2.1%
33. Fatigue	During hospital stay	0%

Table 5.9: Round 2 Ranking results from cardiac arrest survivor and partner participants. In order of percentage of participants including outcome domain ranking 1-5. The outcome domains listed in italics are from patients with higher recall only.

Outcome	Time point	% including in ranking (1-5)
1. Brain function	At hospital discharge	78.9%
2. HRQOL	At hospital discharge	76.3%
3. <i>Brain function</i>	<i>During hospital stay</i>	68.8%
4. Participation	At hospital discharge	60.5%
5. Emotional well-being	At hospital discharge	52.6%
7. <i>Organ function</i>	<i>During hospital stay</i>	50.0%
7. Activities of daily living	At hospital discharge	50.0%
8. Financial impact	At hospital discharge	47.4%
9. Physical symptoms	At hospital discharge	39.5%
11. <i>Family impact</i>	<i>During hospital stay</i>	37.5%
11. Family impact	At hospital discharge	37.5%
13. <i>Emotional wellbeing</i>	<i>During hospital stay</i>	31.3%
13. <i>Physical symptoms</i>	<i>During hospital stay</i>	31.3%
14. Fatigue	At hospital discharge	23.7%
15. <i>Side effects</i>	<i>During hospital stay</i>	15.8%
17. <i>Health related quality of life</i>	<i>During hospital stay</i>	12.5%
17. <i>Activities of daily living</i>	<i>During hospital stay</i>	12.5%
19. Cost effectiveness	At hospital discharge	2.6%
19. Discharge location	At hospital discharge	2.6%
22. <i>Duration of stay in intensive care</i>	<i>During hospital stay</i>	0%
22. <i>Duration of stay in hospital</i>	<i>During hospital stay</i>	0%
22. <i>Fatigue</i>	<i>During hospital stay</i>	0%

All participant groups

Round 2 brought together consensus on some of the differing views between healthcare professional and patient and partner groups seen in round 1.

Participation within 1 year reached consensus in the patient and partner groups in round 1 and achieved consensus in the healthcare professional group in round 2. Brain function during hospital stay and hospital discharge reached consensus in round 1 in the health care professional groups, brain function at hospital discharge reached consensus and during hospital stay was close to consensus (68.8%) in the patient and partner groups in round 2.

Discrepancies of the importance of a number of outcome domains remained present after round 2. Fatigue within 1 year reached consensus in the patient and partner group round 1 with the same outcome reaching consensus of limited importance in the healthcare professional group in round two. Fatigue during hospital stay was the only common outcome domain between groups reaching consensus of limited importance.

After two rounds of survey 25 outcome domains (12 health domains across a range of time points) reached high levels of consensus in at least one stakeholder groups. Outcome domains were from the core areas: pathophysiological manifestations (7), survival (5) and life impact (13) and no outcome domains from the core area of economic impact and resource use reached consensus of critical importance. Figure 5.6 illustrates the outcome domains reaching consensus of critical importance across both rounds of

survey and outcome domains close to consensus in round two, in each stakeholder group.

From these results it was concluded that sufficient information was gained from the two rounds of survey to inform the consensus meeting, that a further round of survey was unlikely to provide any additional benefit. Further discussion and reduction of the list of important outcome domains was sought at a consensus meeting.

Figure 5.6: Outcome domains reaching high levels consensus after two rounds of survey

Core Area	Outcome Domain	<i>During CPR</i>	<i>Immediately after CPR</i>	<i>During hospital stay</i>	<i>At hospital discharge</i>	<i>Within 1 year</i>
Pathophysiological manifestations	Circulatory function	○	●	●▲		
	Respiratory function			▲		
	Renal function					
	Brain function (neurological markers)		○	○▲	●▲	●▲
	Adverse events					▲
Survival	Survival	●	●	●▲	●▲	●▲
Life impact	Physical symptoms				●	●▲
	Activities of daily living				●	●▲
	Health related quality of life				○	●▲
	Emotional well-being					▲
	Family impact					▲
	Participation				△	●▲
	Fatigue					▲
Economic impact and resource use	Cost effectiveness					
	Duration of stay in hospital					
	Duration of stay in intensive care					
	Financial impact to an individual and family					
	Discharge location					

Key: >70% R1 or R2: ● Healthcare professions researchers ▲ Patients and partners

>60% round 2 : △ Healthcare professions researchers ○ Patients and partners

Boxes that greyed out were rated or ranked on their importance.

5.4. Discussion

Key findings

This study is the first to explore the importance of different outcome domains reported across the cardiac arrest journey to an international audience key stakeholders including healthcare professionals, researchers, patients and their partners. From an initial total of 43 outcome domains (plus 5 outcome domains introduced in round 2), two rounds of Delphi survey supported a reduction in this number to 25 outcome domains from three core areas – survival, life impact and pathophysiological manifestations for which a high level of consensus (70% in round 1 or more than 60% in round 2) of critical importance in healthcare professional/researcher and/or patient/partner groups was achieved.

These outcome domains were: circulatory function during CPR, immediately after CPR and during hospital stay (3); brain function immediately after CPR, during hospital stay, at hospital discharge and within the first year (4); adverse events within the first year (1); survival at all five time points (5); physical symptoms, activities of daily living, HRQoL and participation at hospital discharge and within 1 year (8); and emotional wellbeing, family impact and fatigue within 1 year (3).

These findings highlight discrepancies between the outcomes reported in cardiac arrest RCTs and what key stakeholders view as the most important. 11 outcomes from the core area life impact and 10 outcome domains assessed after hospital discharge reached high levels of consensus in a

least one stakeholder group, both of these concepts had limited focus in current outcome assessment in RCTs.

Strengths and limitations

The findings of this study are informed by the view of internationally diverse multiple stakeholders (healthcare professionals, researchers, patients and their partners): with a total of 168 participants from 15 countries participating in round 1. Traditionally smaller groups of healthcare professional and researcher views have been considered, notably without the incorporation of the views of patients as participants in consensus development exercises in the field of cardiac arrest research and registry recommendations (Becker et al., 2011, Perkins et al., 2014).

Recruitment in round 1 was high with 99 healthcare professionals or researchers and 69 patients or partners participating, just exceeding the target total of 150 participants. Survey completion was high (85% starting the survey). The involvement of multiple stakeholder groups in the design and piloting of the survey improved the acceptability, readability and relevance of the questionnaire. Despite multiple email reminders a target completion rate of 80% in round 2 was unachievable with rates of 55.6% and 62.3% for the healthcare professional and researcher group, and the patient and partner group respectively. This puts the results of round 2 at a risk of bias (Hsu and Sandford, 2007a).

One reason for the lower attrition rate may be the snowballing nature of the survey. Despite the snowballing approach allowing large numbers of participants in round 1, a limitation was that initial invitations and encouragement of participation were sent by a known contact to participants in round one, but in round two the invite was sent from the study team. The study team email may not have been recognised by participants and participants may have felt less obliged to complete (Hsu and Sandford, 2007a). It may be possible that participants did not fully understand that they would be expected to participate in a second survey, in round 1 instructions encouraged invitees to participate if they were willing to participate in more than one round of survey.

Whilst a strength of this study was the international representation of views, a limitation, common to many Delphi surveys, was the absence of survey cross cultural and translational validation. The survey was developed for completion by participants who were proficient in English. Although the steering group included international participants, a rigorous evaluation of the cross- cultural transferability of outcome domains was not undertaken. In the second round of survey where the approach changed there were a number of completion error from healthcare professional and researchers (n=8). These errors have resulted from the instructions not being sufficiently understood.

A strength of this study is the breadth of professional participants in the Delphi survey including: physicians, allied health professionals, nurses and

academics. This group was predominately physicians (48.4%). There may have also been a large contribution from paramedics, with a 11.6% of participants selecting their occupation as 'other' which may be accounted by a number of paramedic participants from countries where allied health professional is not a familiar term. There was a minority of academics (6.3%) however it is common for academics to have dual roles as clinical professionals. The breadth of participants means that participants may have multiple in cardiac arrest research or care and at different time points of the patient journey. However, some professionals such as health economists and regulators were not included.

Different professions have variable exposure to time points of the patient journey which may determine the importance of outcome domains. For example, paramedics are likely to have contact with patients in the acute stage of patient care where as physicians and nurses may see a patient across a wider time frame influencing views on the importance of outcomes. It would have been beneficial to have included a question where participants self-defined their role and disclosed the stages of patient care their role or research is focussed at to further understand the influence this may have on voting.

Conducting research with both healthcare professionals/researchers and patient/partner groups is complex. Differences in experience and knowledge may influence individuals' abilities to inform a judgement on the importance of outcome domains. It was considered whether patients should be asked

about the importance of the core area pathophysiological manifestations which their understanding may be limited. Likewise, it was considered whether healthcare professionals should be about the importance of the core area life impact, due to differences in ability to understand the importance of outcomes having a longer term life impact to patients. After careful consideration outcome domains listed across the two surveys were kept homologous. However, the unique nature of unconsciousness during a cardiac arrest and differing levels of recall of time spent in hospital, resulting in patients and partners' not being asked about the importance of outcome domains at certain time points.

Healthcare professional and researcher participant group results were collected and analysed separately in order to better understand the differences in view in outcome domains that are the most important to each stakeholder group. It became a challenges to keep surveys homogenous due to the complex nature of cardiac arrest and incorporating different time points, including periods where the patient is unconscious. In addition to this it would have been better research practice to provide both stakeholder groups with scientific and lay terms, during planning this was decided against to keep the surveys at simple as possible.

Patient and public involvement and healthcare professional/researcher piloting, highlighted the importance of 'when' outcome domains considered for COS inclusion should be measured. It is well informed that in core outcome set development, 'what' to measure as part of a core domain

outcome set is the first step, followed by 'how' to measure core domains and defining a core outcome measurement set. However, it is unclear when to discuss the 'when' to measure and current guidance suggests this is part of 'how' to measure (Williamson et al., 2012b), consultation with stakeholders disagreed with this with the time point of measurement influencing to 'what' is being measured and therefore determining the importance.

Strengthening the modified Delphi survey was the response to the high number of outcome domains reaching consensus in round 1, resulting in a change to a ranking exercise. Despite a 9-point rating scale in round 1 to encourage discrimination of the importance 61% of healthcare professional and partners and 56% of patients and partners scores were within the region of critical importance. A change in approach this was important in order for the modified Delphi survey to produce a shorter list of the most important outcome domains to consider further at the consensus meeting. The adaptive nature between rounds of the Delphi helped gained the most valuable information from participants whilst maintaining interest between rounds, with a clearer indication of the importance (and lack of importance) of items not reaching consensus in round 1. On reflection it would have been advantageous to include those reaching importance of critical importance in round one to see if the ranking exercise influenced results.

Conclusion

The results of this international and multiple stakeholder modified Delphi survey highlight many outcomes judge as most important to various

stakeholders are not currently reported in cardiac arrest randomised controlled trials. An important finding of the modified Delphi results was the importance of capturing the longer term life impact of cardiac arrest survivors which currently not captured in RCTs in this research field.

Resulting from this modified Delphi survey 25 outcome domains listed across the patient trajectory were further discussed on their importance and potential inclusion as part of a COS.

Chapter 6: Consensus

development on the most

important outcome domains: An

International consensus meeting

6.1. Introduction

This chapter describes the final stage in the development of a Core Domain Set (CDS) for cardiac arrest clinical trials. This chapter details an international consensus meeting which sought to reduce the number of outcome domains to a minimum number, and hence define a CDS for cardiac arrest effectiveness trials. Section 6.2 describes the steps that took place in preparation for and at the meeting. Section 6.3 summarises the meeting discussion points on the importance of outcome domains, the voting results and discussion points on how to measure important outcome domains. The chapter concludes with a summary of the findings and findings in the context of other research.

Aims:

1. To achieve international consensus on the outcome domains to include in a core domain set (CDS) for cardiac arrest effectiveness trials.
2. To commence exploratory discussions to define how the nominated outcome domains should be assessed, and hence inform development of a core outcome measurement set (COMS).

6.2. Methods

Chapter 2 provided a synthesis of consensus development methods and justification for the decision to undertake a two-stage consensus development process for the COSCA study: first, the international Delphi survey (chapter 5); and second, the face-to-face consensus meeting detailed in this chapter.

6.2.1. Participants

Stakeholder participation

Consensus was sought from a group of international experts in resuscitation research and practice, including: healthcare professionals, academics, and survivors of cardiac arrest and their representatives.

Previously in COS development OMERACT have held meetings with participants from a range of stakeholder groups (Kirwan et al., 2003, Mease et al., 2009, Kirwan et al., 2007). In COS development other studies have included separate meetings or additional meetings for healthcare professional and researcher groups and patient and public groups (Potter et al., 2015a). For the COSCA study it was important a range stakeholders were present at the same meeting to ensure the view of patients was considered throughout COS development and to seek convergence of stakeholder views.

Inclusion and exclusion criteria

Eligibility criteria for participation in the consensus meeting was defined as follows:

- *Experienced healthcare professionals* currently involved in the provision of care for cardiac arrest patients, intensivists, paramedics, emergency physicians, cardiologists, nurses and rehabilitation specialists.
- *Experienced academics* defined by a history of publication in the field of cardiac arrest research.

- *Adult survivors of cardiac arrest* who had not sustained cognitive impairment as a consequence of the arrest, and hence were able to participate in a group discussion.
- *Partners of the survivors* of cardiac arrest
- *Patient advocates* with experience of resuscitation research.
- All participants were over the age of 18 and fluent in English

Sample size

COS developers have reported a range of participant numbers in face to face consensus meetings, including between 14 participants in a consensus meeting for the development of a CDS for children with cleft palate (Harman et al., 2015) to 43 for a CDS for eczema (atopic dermatitis) (Schmitt et al., 2010). However, the majority of studies report between 25-30 voting participants (Potter et al., 2015a, McGrath et al., 2008, Turk et al., 2003, Saketkoo et al., 2014b).

A target of between 20 and 30 voting participants was sought for the COSCA consensus meeting. Good practice guidance from OMERACT suggests that 10% of the total consensus group should be patients participants (Boers et al., 2015). Alternative guidance for the mix of patient participants with other stakeholders in such meetings is not available. Therefore, COSCA sought to invited between 4-5 patient participants, approximately 20% of the required total group of 20-30.

Recruitment

Identifying participants

The consensus meeting was linked to an international resuscitation meeting – the European Resuscitation Council Congress: New Guidelines, held in Prague (October, 2015). The meeting included international participants from Europe, North America, Australasia and Asia, and this was an opportunity to host a meeting with international stakeholder participants at minimum inconvenience and cost. The consensus meeting was intended to be internationally representative, and hence participants were invited from six continents (Europe, North America, South America, Australasia and Asia), with the aim of at least one representative from each continent. Conference attendees sought to attend the consensus meeting included ILCOR taskforce members, ERC Board of Council members and ERC working group member, indicating expertise in this field. Potential healthcare professionals and researchers were identified from existing contacts from the steering group, different clinical occupations and research interests were sought. Patients, patient's relatives and patient advocates were identified through established relationships with the COSCA study team members and the Resuscitation Council UK (RCUK) patient advocate group.

Approach to participants

A formal email invitation to participate in the COSCA consensus meeting, including detailed information about the meeting (appendix 6.1), was sent to all potential participants. From existing contacts 28 healthcare professionals or researchers from 12 countries were invited to attend the meeting. A total

of 5 patients, patient's relatives and patient advocates were invited to attend the meeting.

Ethical considerations

This meeting was approved by the ethics committee (REC number 13/WM/0464) and amendment was approved based on the change of location was approved on 29.06.16.

Considerations at the meeting were made to ensure patient and public representatives were well informed and integrated as meeting. To aid understanding all participants were provided with sufficient information about the study in advance of the meeting. Patient and public participants met with the core steering group before the meeting to ensure they understood what was required of them, the purpose of the meeting, what to expect and to feel comfortable at the meeting.

At the start of the meeting, all participants were advised to be respectful of each other and that every view was valid. Participants were also encouraged to avoid jargon and to use language that would be acceptable to the lay participants. Written consent was not obtained at the meeting owing to the fact there was no identifiable data obtained. Discussions notes were taken to inform the reporting of discussion points and voting was anonymous.

Travel, accommodation and sustenance expenses were covered for patient and public participants. For healthcare professional and researcher

participants already attending the ERC conference expenses for their accommodation in order to attend the COSCA meeting were covered.

6.2.2. Consensus process

This section describes the pre-meeting information circulated to participants and the structure of the COSCA consensus meeting.

6.2.2.1. Pre-meeting information

Experience has highlighted the importance of a strong, independent chair in the running of a consensus meeting (Haywood et al., 2014a, de Wit et al., 2013a). Professor Vinay Nadkarni (VN) was the invited chair for the meeting. As co-chair of ILCOR, Professor Nadkarni is well-known to the resuscitation community, with extensive experience of chairing consensus meetings in this field (Becker et al., 2011, Perkins et al., 2014). To ensure clarity and consistency in defining the goals for the meeting, monthly meetings were held between the lead researcher (LW), primary PhD supervisor (KH) and Professor Nadkarni during the 6 months leading up the consensus meeting.

An evidence synthesis of the methods included prior to the consensus meeting were circulated to meeting participants two weeks before the COSCA meeting. This included: 1) the systematic review of outcomes reporting in cardiac arrest randomised controlled trials (Whitehead et al., 2015) (chapter 3); 2) the results from interviews with survivors of cardiac arrest and their partners (chapter 4); and 3) the result of the international

modified-Delphi survey (chapter 5) (Appendix 6.2). The primary aim of the meeting was highlighted, to define a CDS.

Although the primary aim of the meeting was to develop a CDS, the intention was to commence discussion towards defining a COMS; with this intent, participants were invited to consider any additional evidence or experience in relation to the measurement or assessment of health outcomes that may be of relevance to the meeting.

6.2.2.2. Meeting structure

The COSCA meeting was held on the afternoon of the 28th of October (12:30-17:00) and the morning of the 29th of October 2015 (08:00-12:00), replicating a one-day meeting but allowing time to reflect on discussion points. Day 1 focussed on defining a core domain set (CDS) - which outcomes should be measured. Day 2 explored unresolved issues from day 1, and the development of a core outcome measurement set (COMS) – how to assess outcomes. The meeting discussion explored outcome domains categorised within the OMERACT 2.0 framework (previously described in chapters 1 and 4).

Plenary presentation

The meeting began with introductions, an overview of the meeting structure, and aims and a presentation of the research findings presented in the pre-meeting evidence synthesis with the opportunity for questions. Both days 1 and 2 began with large group discussions before breaking into smaller group

discussions, which fed back to the larger group before interactive voting ending both days. An overview of the meeting structure is described in figure 6.1. To assist the small group discussions facilitators were identified in advance of the meeting for their experience and expertise relevant to the four core areas to be considered for the CDS:

- Pathophysiological manifestations: Prof Gavin Perkins (GP) – clinical academic, trialist and expert in CA research;
- Survival: Michael Smyth (MS) – a paramedic academic
- Life Impact: Laura Whitehead (LW) – PhD student.
- Economic impact and resource use: Dr Kirstie Haywood (KH) – academic (health measurement and COS development) and Dr Felix Achana (FA) – health economist.

Facilitators' had the roles of: encouraging participation of all group members; keeping discussions on topic; and bringing together the key messages from group discussions.

Small and large group discussions

Participants were pre-organised into four breakout groups to ensure that each group included participants of different nationalities, genders and research backgrounds. After consulting patient representatives, one patient representative was allocated to each group to allow for a wider understanding and integration of their views.

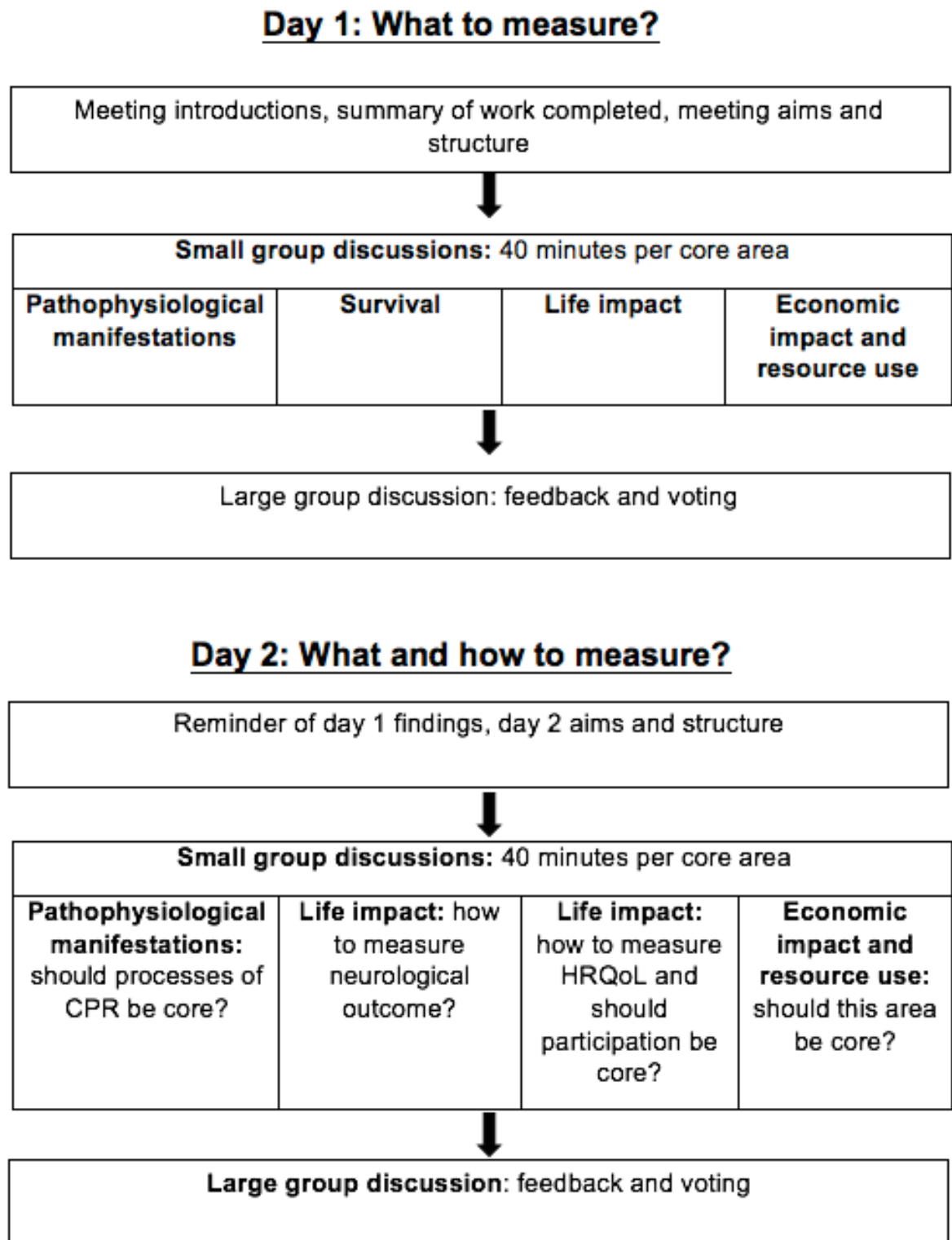
Consecutively, each group was invited to independently explore potential outcome domains within each of the four core areas: 1) Pathophysiological manifestations– facilitated by GP; 2) Survival– facilitated by MS; 3) Life impact – facilitated by LW; and 4) Economic impact and resource use – facilitated by KH and FA.

Each discussion round lasted for up to 40 minutes; each group nominated a note-taker. On day two the same breakout groups were applied and the content of group discussions was informed by the results of day 1 voting, focussing on whether outcome domains close to consensus or raising debate should be included in the CDS and how to measure outcome domains reaching consensus on day 1.

Core area facilitators rotated between groups, providing a brief synthesis of key messages from discussions with previous groups before feeding back to the larger group. An iterative approach to the meeting structure allowed the inclusion of outcome domains suggested by participants. This process supported groups in developing their thinking and responding to the views of other groups.

Once all groups had discussed each core area a larger group discussion occurred. Facilitators fed back key points for discussions on the core area they were responsible for, participants had the opportunity to further contribute to the summary in the larger group setting. After large group discussions voting procedures were explained and voting occurred.

Figure 6.1: Overview of the COSCA meeting structure



Core area discussion content

Small group discussions at the meeting were informed by the results of the modified Delphi survey where 25 outcome domains (12 health outcome domains at a range of time points) reached high levels of consensus. An alteration was the domain of brain function, splitting into brain function (pathophysiological manifestations) and cognition and consciousness (life impact). Additionally, two further outcomes were introduced resulting from consensus meeting participant comments. Despite not reaching high levels of consensus in the modified Delphi, it was decided economic evaluation and resource use should be discussed further at the meeting. Alterations and additions resulted in a total of 30 outcome domains (17 health outcome domains at a range of time points) being considered at the consensus meeting (Figure 6.2).

Figure 6.2: Outcome domains discussed at the COSCA meeting

<u>Core Area</u>	<u>Outcome Domain</u>	<i>During CPR</i>	<i>Immediately after CPR</i>	<i>During hospital stay</i>	<i>At hospital discharge</i>	<i>Within 1 year</i>
Pathophysiological manifestations	Circulatory function	○	●	●▲		
	Respiratory function			▲		
	Renal function					
	Brain function (neurological markers)		○	○▲		
	Adverse events					▲
	Process measure of CPR *					
Survival	Survival	●	●	●▲	●▲	●▲
Life impact	Consciousness and cognition		○	○▲	●▲	●▲
	Physical symptoms				●	●▲
	Activities of daily living				●	●▲
	Health related quality of life				○	●▲
	Emotional well-being					▲
	Family impact					▲
	Participation				△	●▲
	Fatigue					▲
Economic impact and resource use	Cost effectiveness					
	Hospital free survival *					

Key for figure is on the next page

Figure 6.3 Key:

>70% R1 or R2: ● Healthcare professions researchers ▲ Patients and partners

>60% round 2 : △ Healthcare professions researchers ○ Patients and partners

Boxes that greyed out were rated or ranked on their importance. * Adapted or newly introduced.

Voting and consensus development

To inform voting decisions, participants were provided with a paper version of the tabulated results from the Delphi survey. This in turn reflected the order in which the outcome domains were presented during the voting process and provided a template for the distribution of their votes, this did not include outcomes introduced at the meeting (Appendix 6.3),

Each outcome domain was individually presented on a large screen, with the voting options listed (Yes or No for inclusion in the CDS). From a total number of outcome domains considered on day 1 of 29, participants were advised to vote 'YES' for a maximum of 7; they could vote for fewer if they so wished. They were instructed to vote 'No' for all outcome domains they did not wish to be included in the CDS. Informed by other COS development, a high level of consensus was set at 70% agreement to include the core domain set (Boers et al., 2015, Harman et al., 2015, Schmitt et al., 2012, Haywood et al., 2014a). Voting was restricted to maximum of 7 outcome domains to ensure participants were voting for outcome domains they viewed as essential across trials. This was informed by concerns raised by recent COS including a large number of outcome domains. OMERACT raise that a COS should include no more than 9 outcomes and Cochrane

summary of findings tables allow up to 7 outcome domains to be included (Boers et al., 2015, Langendam et al., 2013).

On day 2 outcome domains which scored high levels of consensus and raised discussion points before voting on day 1 were further discussed about their importance for CDS inclusion and were re-voted on. Day 2 votes for CDS inclusion (Yes or No) occurred for 5 outcome domains with no restriction on the voting.

Participants voted by means of individual voting keypads; votes were recorded with the use of TurningPoint software (Turning Technologies, Youngstown, Ohio, USA). The software provided real-time feedback allowing manual recording of results alongside the automatic electronic recording of votes. To support a retrospective exploration of differences in voting between the patients and partners and the wider group, the former were allocated identifiable voting keypads as a group. With the exception of the chair and facilitators, all participants had voting powers that were weighted equally.

6.3. Results

6.3.1. Participants

From a total of 28 clinicians and healthcare researchers from 12 countries invited to participate in the COSCA consensus meeting, 19 (73%) attended, representing 11 countries (UK, the Netherlands, Germany, Belgium, Sweden, Finland, USA, Canada, Singapore, Australia and New Zealand). The majority were naïve to the COSCA study, a small number (n=5) had previously provided insight to study design or participated in the Delphi survey. Participants with academic and clinical backgrounds were physicians (13), nurses (2) and allied health professionals (2). Participants had involvement/or research interests at one or more time points across the cardiac arrest trajectory including prehospital care (12), during hospital care (15), post hospital discharge (3) and completed qualitative research or patient and public involvement (3). Two confirmed attendees having a research focus on survivors in the post hospital discharge were unable to attend the meeting.

The patient representatives included two cardiac arrest survivors (both female), one partner of a survivor, and one patient advocate – all from the UK, and representing 17.4% of the voting participants. The patient representatives attending the consensus meeting had not participated or been involved in previous steps in the COSCA study (interviews, modified Delphi survey or study design). All participants attended the full duration of the consensus meeting.

6.3.2. Developing a Core Domain Set (CDS) and exploring a Core Outcome Measurement Set (COMS)

The results will be presented for each core area: 1) Pathophysiological manifestations; 2) Survival; 3) Life impact; 4) Economic impact and resource use. Within each core area key discussion points of how to assess core outcome domains will be presented.

6.3.2.1. Pathophysiological manifestations

Day 1: Pathophysiological manifestation discussion summary

Consensus meeting participants were invited to consider the importance of seven outcome domains from the core area pathophysiological manifestations: circulatory function during CPR; circulatory function immediately after CPR; circulatory function during hospital stay; respiratory function during hospital stay; brain function (neurological markers) immediately after CPR; brain function (neurological markers) during hospital stay and adverse events within 1 year.

There was general agreement that the assessment of various pathophysiological manifestations, such as circulatory function and respiratory function, are important during the early stages of a patient's journey, but become less important once a return of spontaneous circulation (ROSC) has been achieved. There was also agreement that such measures are specifically important to trials where the focus is on the evaluation of new interventions and advancing discovery. However, there was general

agreement that the importance of assessing pathophysiological manifestations across the wide range of trials in this field is more limited.

There was discussion about the potential for pathophysiological measures to act as surrogate assessments for longer-term functional outcomes. For example, it was suggested that Neuron-Specific Enolase (NSE) could be a useful surrogate measure to predict the impact of an arrest on longer term neurological outcome and survival (Calderon et al., 2014, Einav et al., 2012). However, little evidence was available to support these suggestions; further exploration of any association is required before recommendations could be considered.

The importance of reporting adverse events was discussed at length. There was agreement that adverse event reporting in effectiveness trials should adhere to good clinical practice guidance. Moreover, adverse events are likely to be specific to an intervention; it was agreed that adverse event reporting would not be beneficial as a core outcome for cardiac arrest effectiveness trials but essential as part of study documentation.

Day 1: Pathophysiological manifestation voting

Consensus was not achieved for the inclusion of any of the seven original outcome domains from this core area (Table 6.1). In addition to the outcome domains reaching a high level of consensus in the modified Delphi survey, the outcome domain 'processes of CPR' was raised as important by meeting participants supporting further discussion and inclusion in the day 1 voting

exercise. 'Processes of CPR' included CPR quality measures such as: compression depth, compression rate and time to intervention.

'Processes of CPR' were identified in the systematic review but were not included in the modified Delphi survey, the reason being that processes of CPR had been perceived as a measure of care provided rather than an outcome assessment by the steering group. In day 1 voting a moderate level of consensus achieved (56.5%), the group expressed a desire to continue the discussion about this outcome domain on day 2.

Day 2: Pathophysiological manifestation further discussions and voting

There was general agreement that measures reflective of the 'processes of CPR' such as: compression depth, compression rate and time to intervention, are important due to their potential to influence study outcomes. However, whilst essential indicators of the quality of systems or as indicators of potential confounding factors and understanding the impact of interventions, it was concluded that they should not be considered as a core outcome domain for effectiveness trials. However, this does not mean processes of CPR are not important and shouldn't stop trialists from reporting as outcomes in trials where appropriate. A further vote failed to support inclusion of Processes of CPR in the CDS (17.4%) (Table 6.1).

Table 6.1: Consensus meeting voting results day 1 and 2

Outcome domain	Time point	Day 1 voting	Day 2 voting
<i>Pathophysiological manifestations and processes of CPR</i>			
Circulatory function	During CPR	0%	
	Immediately After CPR	0%	
	During hospital stay	4.4%	
Respiratory function	During hospital stay	0%	
Brain function	Immediately After CPR	4.4%	
	During hospital stay	4.4%	
Adverse events	Within 1 year	8.7%	
Process of CPR	During CPR	56.2%	17.4%
<i>Survival</i>			
Survival	During CPR	17.4%	
	Immediately After CPR	43.5%	52.2%
	During hospital stay	8.7%	
	At hospital discharge	91.3%	Day 1 consensus
	Within 1 year	21.7%	
<i>Life impact</i>			
<i>Neurological outcome*</i>	Immediately After CPR	8.7%	
	During hospital stay	4.4%	
	At hospital discharge	78.3%	Day 1 consensus
	Within 1 year	39.1%	
Physical symptoms	At hospital discharge	4.4%	
	Within 1 year	0%	
ADL	At hospital discharge	8.7%	
	Within 1 year	17.4%	
HRQOL	At hospital discharge	34.8%	
	Within 1 year	82.6%	Day 1 consensus
Emotional wellbeing	Within 1 year	17.4%	
Family impact	Within 1 year	8.7%	
Participation	At hospital discharge	0%	
	Within 1 year	30.4%	8.7%
Fatigue	Within 1 year	13.0%	
<i>Economic impact</i>			
Economic factors	-	39.4%	21.7%
Hospital free survival 30 days?	-	-	21.7%

6.3.2.2. Survival

Day 1: Survival discussion summary

Survival is an important outcome in cardiac arrest research and can be measured at numerous time points, and by various definitions (Whitehead et al., 2015). In chapter 3, 39 different measures of survival were reported including: survival to hospital discharge, survival to hospital admission and 11 different measurements of Return of Spontaneous Circulation (ROSC). In the modified Delphi Survey (chapter 5), survival was split across the five time points of the patient journey and a high level of consensus was achieved from both healthcare professionals and patient participants to at all time points. This assessment considered various measures of ROSC, survival during hospital, survival at hospital discharge and at various time points following hospital discharge.

Discussions concluded short term survival, such as ROSC measures are important to advancing discovery in this field but have limited indication of the longer term patient outcome. If ROSC were to be included as a core outcome, a transparent and agreed upon definition would be essential (Whitehead et al., 2015)(Chapter 3). There was general consensus that 'survival to 30 days or hospital discharge' was a feasible measure of survival, providing some indication of patient recovery. However, if used alone, it failed to capture long-term patient outcomes. Moreover, it failed to define discharge location or functional status, in some cultures patients may be discharged to home for a comfortable death.

The time point 30 days or hospital discharge was chosen to be analogous to Utstein definitions, reflecting differences in data collection capabilities of varying systems. It was argued that 30-day survival had some advantages as a fixed measure in comparison to the variable time point of hospital discharge; the pros and cons of each time-frame were debated. However, it was agreed that consistency with the Utstein recommendations (Perkins et al., 2014) was important and the dual time point of measurement was retained to considering the capabilities of different systems.

Day 1 and 2: Survival voting

A high level of consensus was achieved for the inclusion of 'Survival at 30-days / hospital discharge' (91.3%) as a core outcome in the CDS. There was moderate agreement for the assessment of survival immediately after CPR (reported by a sustained ROSC) (43.5%) (Table 6.1). Survival immediately after CPR was therefore considered further during day 2. It was chosen to discuss survival immediately after CPR in the larger group setting as this had been discussed in depth in small group discussions on day 1. Following a second vote, survival immediately after CPR failed to reach consensus for inclusion in the CDS (52.2%) Table 6.1.

6.3.2.3. Life impact

Day 1: Life impact discussion

15 outcome domains (8 health domains across multiple time points) from the core area life impact reached high levels of consensus in at least one stakeholder group after two rounds of Delphi survey (Table 6.1):

Consciousness and cognition immediately after CPR, during hospital stay, at hospital discharge and within 1 year; physical symptoms at hospital discharge and within 1 year; HRQoL at hospital discharge and within 1 year; activities of daily living (ADL) at hospital discharge and within 1 year; participation at hospital discharge and within 1 year; emotional wellbeing within 1 year; fatigue within 1 year and family impact within 1 year.

Consensus meeting participants discussed a number the wide range of outcome domains listed under 'life impact'. It was agreed that changes to cognition and neurological functioning are common and significant concerns for survivors of cardiac arrest. The wide-ranging impact of cardiac arrest on the physical, social and emotional wellbeing of an individual, and the challenge of returning home once discharged from hospital were discussed at length, and reported as embracing important outcomes that should be considered over both the short and long-term patient journey. An approach to assessment that sought to capture the breadth of these domains – a multi-domain approach to assessment, was favoured. The group explored the importance of how new symptoms impacted on and interfered with an individual's ability to function normally – to complete usual activities, to participate in activities that they had enjoyed prior to their arrest – be that employment, socialising or maintaining usual family roles.

Day 1: Life impact voting

At the end of day 1, two outcomes – 'health-related quality of life (HRQoL) within 1 year' (82.6%) and 'Consciousness and cognition at 30 days/ hospital

discharge' (78.3%) reached high levels of consensus for inclusion in the CDS (Table 6.1). There was apparent confusion of the true definition of 'participation'; therefore, the definition and potential for assessment within 1 year was further discussed on day 2.

Further discussion on day 2 in small in large group discussions concluded that 'consciousness and cognition' was more appropriately termed 'neurological outcome.' Consciousness and cognition was selected to reflect terminology of assessment tools which are frequently applied to assess neurological outcome. Attendees raised that neurological outcome reflected current measurement tools and has homologous terminology with the Utstein template.

Day 2 discussion: Core Outcome Measurement Set

Day two discussion explored the suitability of available measure to assess outcome domains for reaching consensus for COS inclusion. Discussions were informed by clinical and research experience rather than an extensive review of the quality and acceptability of measurement tools.

Neurological outcome

Several widely used clinician-completed measures of neurological or functional outcome – specifically, the Cerebral Performance Category (CPC) (The Brain Resuscitation Clinical Trial II Study Group, 1991) the mRS (Bonita and Beaglehole, 1988, RANKIN, 1957) and Glasgow Outcome Scale extended (GOS-E) (Wilson et al., 1998) were discussed at length.

The CPC and mRS are widely used in cardiac arrest effectiveness research (Whitehead et al., 2015), and are recommended as part of the Utstein data reporting recommendations (Perkins et al., 2014). They are both clinician-reported outcome measures, completed as a result of clinician observation, by reference to clinical notes, or through discussion with patients. Both the CPC and mRS are short and quick to complete, providing a simple assessment. The CPC rates 'neurological function' between 1 - good cerebral performance and 5 - death/brain death. A CPC score between 1-2 suggests a good outcome and scores between 3-5 indicating a poor outcome. The mRS rates 'function' between 0 - no symptoms, and 6 - death. Scores assess the level of independence and ability to complete activities in comparison to an individuals' pre-arrest state.

The GOS-E is a measure of functional recovery which considers the outcomes in relation to pre-arrest status. Although a clinical reported outcome, it is designed to be completed with the patient. Scores range between 1 - death, and 8 -good recovery. Outcome is categorised as: death, vegetative state, severe disability (lower and upper), moderate disability (lower and upper) and good recovery (lower and upper).

Despite the advantages of these measurement tools being quick to complete they face criticism with limited information on the psychometric of such tools. A small number of studies have investigated the comparability and inter-rater variability of tools. A prospective longitudinal compared CPC and mRS score

at hospital discharge through chart review of 21 cardiac arrest survivors with interviews at 1 month to determine CPC, mRS and Health Utilities Index (HUI-3) scores (Raina et al., 2008). An important finding from this study was that clinician-based CPC completion informed by clinical notes at hospital discharge reported significantly higher outcome compared to a 1-month face to face completion of the CPC, overestimating patient outcome. Further to another study assessed inter-rater variability in CPC scores of OHCA patient with VF(n=131) assessed by entire hospital record has been explored between three assessors indicating weak agreement (kappa 0.5) (Ajam et al., 2011), raising potential issues with the CPC scale.

Health Related Quality of Life

Group discussion described the wide ranging impact of cardiac arrest including the impact to emotional wellbeing, physical wellbeing and ability to participate in their normal activities. It was agreed that questionnaires, or patient-reported outcome measures (PROMs), which capture the wide-range of outcomes that are important to survivors of cardiac arrest could provide essential information for a COS for CA. However, a PROM specific to the experience of survivors of cardiac arrest does not currently exist. Therefore, discussions focussed on generic measurements of HRQoL: the SF-36(Ware and Sherbourne, 1992), EQ-5D(Rabin and de Charro, 2001) or HUI-3(Furlong et al., 2001). Evidence of such tools performance in the cardiac arrest population is limited. However, a recent publication has highlighted that the EQ-5D assessment of HRQoL produced ceiling effects, limiting its interpretability (Andrew et al., 2016).

Significant concerns were raised about the feasibility of assessing HRQoL post hospital discharge: specifically, obtaining patient consent to continue, non-representativeness of responders, the cost and ease of follow-up assessment.

6.3.2.4. Economic impact and resource use

Day 1: Economic impact and resource use discussion summary

In round 2 of the Delphi survey participants were asked to score the importance of cost effectiveness, duration of hospital stay, duration of stay in ICU, financial impact and discharge location. Although domains reflective of this core area were not shortlisted by participants in the Delphi survey, the importance of this core area in the OMERACT 2.0 framework suggested that further discussion of the relative importance of this core area and possible domains was required. Group discussions held during day 1 of the consensus meeting resulted in outcome domains being merged into the over-riding concept of 'economic evaluation'. On day 2 hospital free survival was added as an outcome domain for consideration in the voting process.

Economic evaluation is important when seeking to understand the implementation of interventions within the capacity of a healthcare system, and whether the costs associated with an intervention are beneficial to society and individuals. Group discussion highlighted the complexities of

capturing sufficient information to allow for a full economic analysis of healthcare interventions.

Day 1 and 2: Economic impact and resource use voting

Votes for the inclusion of economic evaluation as part of the CDS reached a moderate level of consensus (39.1%) (Table 6.1). Following further consideration on day 2, votes failed to support inclusion of economic evaluation (21.7%) or hospital free survival (21.7%) as a core domain (Table 6.4). However, it was recommended that all future studies should consider cost effectiveness analyses.

Stakeholder groups

Allocation of voting devices allowed retrospective evaluation of different stakeholder groups voting on day 1. Core outcome domains included in patient and public representative votes (n=4) are compared to collective group votes (n=23). All four patient and public representatives voted for survival at hospital discharge/30days (100%: 91.3%) and three voted for neurological outcome at hospital discharge/30days (75%:78.3%). A discrepancy with the core outcome domains was that only 1 patient and public stakeholder voted for the inclusion of HRQoL of life within 1 year, however 3 voted for the inclusion of HRQoL at hospital discharge.

Differences between stakeholder groups included activities of daily life at hospital discharge, physical symptoms at hospital discharge and adverse events. In each of these outcome domains two patient and partner

representatives votes for these outcome domains but no healthcare professionals or researchers voted for these outcome domains.

6.4. Discussion

Key findings

Consensus was reached on the inclusion of three core outcome domains for the core outcome set for cardiac arrest effectiveness trials: 1) survival to 30 days /hospital discharge, 2) neurological outcome at 30 days/hospital discharge and 3) health related quality of life within 1 year. It is recommended that, as a minimum, these three domains should be considered for routine reporting in future cardiac arrest effectiveness trials (Figure 6.2). These outcome domains capture key factors considered essential in defining a successful resuscitation, that is the patient surviving with no cognitive impairment and an acceptable quality of life (Beesems et al., 2014).

A two-stage process is recommended for COS development (Williamson et al., 2012b). First, defining the CDS: this was the focus of this thesis and was achieved with the consensus meeting detailed in this chapter. Second, defining the core outcome measurement set (COMS) to reflect the CDS: although not the focus of this thesis, participants brought expertise and experience to inform discussion around 'how' the CDS could be measured.

Good practice development in COMS development requires a literature review of evidence in support of the choice of measurement. Potential outcome measures should be truthful, discriminative and feasible (Boers et al., 2014c). Moreover, the relevance and acceptability of potential methods of assessment should be explored with relevant stakeholders (Staniszewska et al., 2012, Prinsen et al., 2014). Initial discussion occurred on how to best assess core outcome domains, however this discussion was driven by participant knowledge and experience rather than an evidence based approach.

Core outcomes are expected to be reported across cardiac arrest effectiveness trials alongside additional study outcomes that are conducted within the premise of good clinical practice (Figure 6.2). Core outcomes and potential assessment tools are discussed:

Survival to 30-days /hospital discharge

‘Survival to 30 days or hospital discharge’ included both the ‘what’ and the ‘how’. The time point of assessment at 30 days or hospital discharge’ was discussed at length. The recommendation reflects a pragmatic choice, underpinned by the need for groups to select the time point judged as most appropriate for their healthcare system, and is consistent with the Utstein template (Perkins et al., 2014).

Neurological outcome at 30-days/ hospital discharge

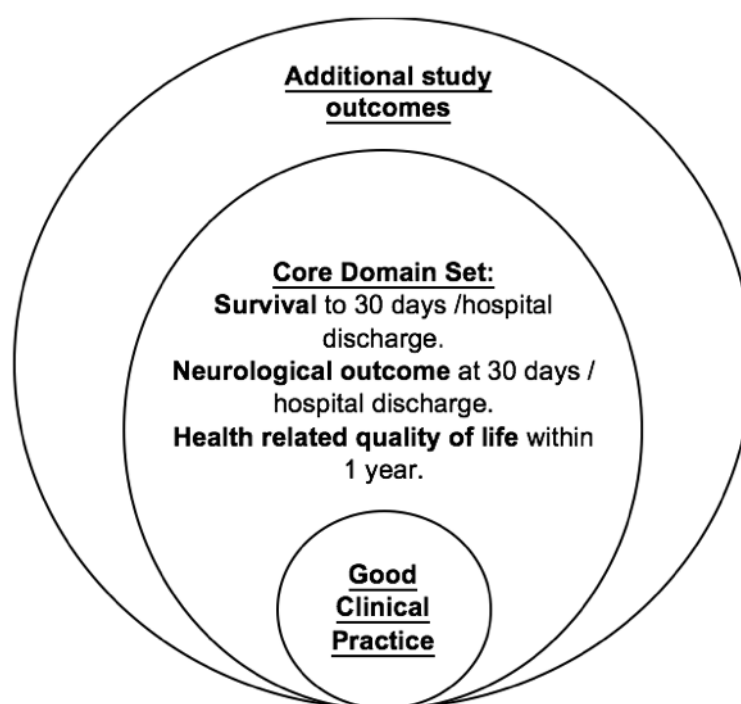
This recommendation reflected current practice – in research (Whitehead et al., 2015), registries (Perkins et al., 2014, Jacobs et al., 2004) and in practice (group discussion) of using the CPC, mRS or GOS-E as a measure of neurological outcome at 30-days or hospital discharge.

Health related quality of life (HRQoL) within 1 year

The third recommended outcome domain is the assessment of ‘HRQoL in the first year’. However, the specific time point of when to assess HRQoL after hospital discharge within the 1st year was not agreed upon.

Evidence suggests that PROM-based assessment in cardiac arrest clinical trials is very limited (Whitehead et al., 2015), but that significant variation in PROM-based assessment exists within prospective studies – with many ad hoc measures identified (Elliott et al., 2011). However, guidance for the PROM-based assessment of cardiac arrest survivors does not exist and a population-specific measure is not available (Whitehead et al., 2015, Haywood et al., 2014b). Discussions did not consider the issues surrounding and potential need for proxy completion. Initial guidance suggests trialists should consider the application of generic measures of HRQoL: the SF-36, EQ-5D or HUI-3.

Figure 6.2: Core domain set in the context of other study elements



The outcome domains reaching consensus for core outcome set inclusion represent the most important across stakeholder groups: healthcare professionals, researchers, patient and partner representative views. This may mean that the most important outcome domains to individual stakeholders may not be captured. For example, health related quality of life broadly assesses patient outcome but may not focus on the aspects most important to survivors of cardiac arrest. Meeting discussions and results highlight the importance of patient centred outcome assessment, but also highlighted the challenges of such reporting including cost and feasibility of assessment completion.

Strengths and limitations

The findings of the meeting are further supported by an extensive evidence synthesis described in previous chapters to inform this meeting. Great efforts were taken to first identify outcome domains that could be potentially included as part of a core outcome domain set and identifying discrepancies in current outcome reporting and the outcomes that matter the most to patients who have survived a cardiac arrest. Synthesised evidence including early consensus development in a modified Delphi survey, provided consensus meeting attendees evidence of the most important outcome domains to large number of different stakeholders of cardiac arrest effectiveness trials from an international background.

However, despite extensive efforts to create a list of potential outcome domains, a number of oversight decisions made by the steering group that were highlighted from group discussion. Firstly, confusion between terminology existing within the area of brain function between, cognition consciousness and neurological outcome. This confusion was caused due to varying terminology and attempts to reflect components of measurement tools.

Secondly a point raised participants was the inclusion of processes of CPR, excluded by COS development team in the early stages as a consideration of study documentation rather than an assessed outcome. This was later excluded from the CDS by meeting participants concluding that this was important as part of study documentation, but on reflection this should have

been a decision that was agreed by the meeting participants rather than the steering group.

International representation at the meeting ensured the consideration of challenges within different healthcare systems. A number of concerns that were raised resulting from differing nationalities included: the restraints of funding bodies; ability to complete data collection post-discharge; the comparability of outcomes between systems (for example economic evaluations); and different requirements and attitudes to good clinical practice. However, it is a limitation that an international patient population was not attainable and this may have reflected differences in care and recovery experience in different countries.

Face to face consensus meetings raise a number of challenges including the dominance of individual participants and individuals' agendas participating in meetings. It is important to acknowledge that each participant from a healthcare professional /research background will have experience and personal interests that may influence their view on the most important outcome domains. For example, trialists may have used particular tools in ongoing and completed studies or may have a role in outcome tool development.

Participants of the COSCA study were not known to have involvement in the development of widely applied measurement tools but participants had a diverse on the importance of and outcome domains and measurement tools.

A number of differences in opinion surrounded legacy measures, historically reported in cardiac arrest research. At times individuals dominated the discussion but the meeting chair retained a balance of views and encouraged participation of individuals in the group discussion seeking to retain a balance of views of participants.

The recommendation on how to best measure core outcome domains, defining a core outcome measurement set is limited. Due to the time and resources available it was not possible to complete a review of the quality and acceptability of potential measurement tools to be included in the COS. Resulting from this an initial recommendation was made on informed by expert attendee knowledge and experience. Now that a CDS has been defined further work will be conducted to best inform trialists how to assess neurological outcome and health related quality of life within this population. It is important that there is standardisation in both what and how outcomes are measured to improve the comparability of future research.

Implications of findings

The next steps of the COSCA research are to develop and begin an implementation plan to results in successful uptake of the CDS. This will include publication of the study findings and the presentation of research at international conferences detailed chapter 7. Currently there is limited guidance for how to achieve successful COS implementation.

Successful implementation of a core outcome set will ensure that cardiac arrest effectiveness trials are reporting outcomes routinely across trials that are relevant to multiple stakeholders. This will increase the comparability and interpretability of future research in this field.

Further steps will be completed to select appropriate measurement instrument to assess neurological outcome and health related quality of life. This will include review of the tools available to assess neurological outcome and health related quality of life in cardiac arrest survivors. Identified tools will be assessed on their quality and acceptability. This will inform a further consensus exercise to define a COMS.

Chapter 7: Summary and discussion

7.1. Introduction

This PhD aimed to develop a Core Outcome Set for future effectiveness trials in cardiac arrest research. The methodological considerations, specific methods and findings for each stage of the study have been discussed in detail in each preceding chapter. This final chapter provides a summary of the main findings, discusses the overall strengths and limitations of the COSCA study and COSCA recommendations, and considers findings in the context of the current state of outcome reporting in cardiac arrest research and COS development more broadly. The implications for future cardiac arrest research are highlighted.

Section 7.2 provides a summary of the key findings of the methods completed as part of the COSCA study and in the context of outcome reporting for cardiac arrest. Section 7.3 discusses the strengths and contribution of this PhD, followed by its limitations in section 7.4. Section 7.5 details future research and dissemination plans. Implications of the findings are discussed in section 7.6, followed by the thesis conclusions in section 7.7.

7.2. Summary of findings

The findings of the four key stages of the COSCA study are summarised: stages 1 and 2 underpin the exploration and definition of outcome domains; stages 3 and 4 describe steps to achieve consensus on which outcome domains should be part of a core outcome set.

7.2.1. Exploring and defining outcome domains

Summary of findings from Stage 1: Systematic review of outcome reporting in cardiac arrest randomised controlled trials

Chapter 3 described the significant heterogeneity in outcome reporting, evidenced by 164 different outcomes reported across the 61 RCTs; and no single outcome was reported across all trials. Many studies reported outcome domains from the core areas of: survival (85%), activities (52.5%), body structure and function (41%) and processes of CPR (26%).

Although the most frequently assessed core area was survival – nine trials did not include survival as an outcome, despite the life threatening nature of cardiac arrest. The exemption of survival as an outcome in some studies may have been due to the sample size, therefore limiting the interpretability of survival as an outcome (Herlitz et al., 2007). The most frequently reported measure of survival was ‘survival at hospital discharge’, reported in 30 trials. Thirty-nine different survival outcome domains (with varying definitions and time point of assessment) were reported, eleven of these were different measurements of return of spontaneous circulation. Reports of heterogeneity in survival outcomes have previously been reported in systematic reviews of outcome reporting in oesophageal cancer (Blencowe et al., 2012) and colorectal cancer (Whistance et al., 2013). When exploring outcome domains to include in a COS, 84 different mortality outcomes were reported in oesophageal cancer studies (Blencowe et al., 2012), and 10 different definitions of post-operative mortality were reported in colorectal cancer studies (Whistance et al., 2013).

Across the 61 trials, no study included the assessment of survivors' health related quality of life or participation. Just one study (Aufderheide et al., 2005) included an ad hoc modification of two existing questionnaires - the Minnesota Living with Heart Failure questionnaire (Rector and Cohn, 2004) and Kansas City Cardiomyopathy Questionnaire (Green et al., 2000) - as a measure of neurological outcome. However, the modification and subsequent impact on the performance of the measure in this population was not reported – suggesting that any data from this measure should be interpreted with caution. Only one other study transparently reported that patients and family were interviewed to support the assessment of activity limitation (Breil et al., 2012). These findings suggest the most important outcomes to patients are unlikely to be assessed in current cardiac arrest RCTs and question whether current measures are providing an accurate assessment of patient outcome.

Since the completion of this review, a small number of large RCTs have been published which have sought to assess patient-centred and patient-reported outcomes to enhance the assessment of the impact of interventions and the quality of survival after cardiac arrest. For example, a large multi-centre trial investigated the effectiveness of targeted temperature management (TTM trial) (33°C vs 36°C) in over 900 cardiac arrest patients. The study reported a primary outcome of all-cause mortality and included assessment of patient centered outcomes (Nielsen et al., 2013). Health related quality of life was included as a tertiary outcome assessed at 6 months with the SF-36v2 (Cronberg et al., 2015). Follow up in survivors was

high in each treatment group (93.5% and 91.9%). Assessment was completed face to face (92.1%) or over the telephone by survivors (92.3% and 91.0% in each treatment group) or proxies (7.7% and 7.1% in each treatment group). Additionally a sub-study analysis of participants of the TTM trial assessed the anxiety and depression of 278 (from 320 eligible) cardiac arrest survivors at 6 months with the Hospital Anxiety and Depression scale (HADS) which were compared to a control group (STEMI patients) (Lilja et al., 2015).

Another study exploring the success of a neurologically focused follow-up intervention with cardiac arrest survivors and their partners included participation in society (Community Integration Questionnaire) and quality of life (SF-36 (8 subdomains) (EuroQoL Visual Analogue Scale (VAS)) at 1 year as primary outcomes (Moulaert et al., 2015). 143 (73%) eligible participants completed the follow up and assessment of outcome. Further patient centered outcomes were reported including emotional function and caregiver strain. These reports of patient centered approach to outcome assessments indicate trialists are becoming aware of the importance of longer term patients centered outcomes.

The review in this PhD highlighted the importance of seeking to improve outcome reporting in future cardiac arrest effectiveness trials and the potential for a core outcome set to assist with this endeavour. It emphasised the importance of seeking to better understand those outcomes that really matter to the survivors of cardiac arrest, reducing the significant

heterogeneity in reporting and improving transparency in the way in which outcomes are selected and reported.

Summary of findings from Stage 2: Qualitative exploration of outcomes important to survivors of cardiac arrest

Current good practice guidance for COS development supports the importance of including multiple perspectives when seeking to define the core outcomes to include (Williamson et al., 2012b). The review of outcome reporting in cardiac arrest research highlighted the lack of patient centrality in outcome reporting. Moreover, there is little qualitative research which seeks to better understand the lived experience of cardiac arrest survivors (Bremer et al., 2009b, Dougherty et al., 2000, Palacios-Cena et al., 2011) and none which specifically seeks to understand what a good outcome – beyond survival - looks like.

Chapter 4 describes the first semi-structured interviews with survivors of cardiac arrest and their partners seeking to identify what really matters to patients in terms of a good outcome, through developing a further understanding of the patients' lived experience. Interviews were conducted with eight cardiac arrest survivors between 3 and 12 months after hospital discharge and with three partners of survivors. An Interpretative Phenomenological Analysis study identified a superordinate theme of survivors experiencing a "disruption to normality". Cardiac arrest survivors viewed their pre-arrest health status as a goal to "get back to normal". Contributing to the "disruption to normality" there were five subordinate

themes: survival; physical function; emotional wellbeing; social wellbeing and participation and the impact to others.

Perhaps unsurprisingly the findings from the interview study highlight discrepancies between what is assessed in current cardiac arrest RCTs and the outcomes that are most important to patients. The outcomes currently reported in published RCTs are likely to be selected by healthcare professionals and researchers, often reflecting the pathophysiological manifestations of an illness, survival or clinician assessment of the impact to functional status. These findings further support the concerns of current outcome reporting largely limited to reporting up to hospital discharge and rarely with assessment completed from the patients' perspective.

The partners of cardiac arrest survivors provided additional, valuable insight into the impact of cardiac arrest. In particular, highlighting the emotional aspects of their partners' journey post-arrest, such as changes in personality and self confidence that the patient may not have been aware of or be willing to convey. There were no major discrepancies in accounts between patients and partners; rather, the partners further supported themes identified from the patient accounts.

The interview findings highlight that current RCTs in cardiac arrest research, currently fail to report a number of the outcomes that are important to patients. There is a great need to incorporate outcome domains that are important to patients into cardiac arrest research.

7.2.2. Achieving consensus on the most important outcome domains

Summary of findings from Stage 3: An international modified Delphi survey

An international modified Delphi survey was conducted to explore the views of multiple stakeholders: health professionals and researchers, cardiac arrest survivors and their partners, to explore the most important outcome domains to include in cardiac arrest research. The two-round survey sought to reach consensus on the most important outcome domains to include in a COS for cardiac arrest research.

Participants were invited to rate up to 43 outcome domains (13 health domains across a range of time points) on their importance to decision-making/patient recovery using a 9-point GRADE scale. The list of outcome domains was informed by the systematic review and interview study findings. After many outcome domains reached high levels of consensus a change in approach was taken in round 2, where participants were invited to rank top outcome domains that did not reach critical consensus ($\geq 70\%$ of scores 7-9 and < 15 of scores 1-3) and five outcome domains added to the survey in response to comments in round 1.

After the two rounds of survey 25 outcome domains (12 health domains across a range of time points) reached high levels of consensus. Outcome domains were from the core areas: pathophysiological manifestations (7), survival (5) and life impact (13). No outcome domains from the core area of

economic impact and resource use reached consensus of critical importance.

Views between stakeholder groups were similar with 11 outcome domains reaching high levels of consensus across stakeholder groups. Three outcome domains (plus 5 at time points excluded from the patient survey) reached high levels of consensus in the healthcare professional and researcher group only; and a further 6 outcome domains in the patient and partner group only. A notable discrepancy stakeholder group views was the importance of fatigue within 1 year, which reached consensus of critical importance in the patient and partner group but conversely reached consensus of limited importance in round 2 in the healthcare professional and researcher stakeholder group. Understanding the importance and assessment of fatigue in cardiac arrest survivors requires further research attention and understanding.

The survey illustrated significant discrepancies between the outcome domains reported in current randomised controlled trials (chapter 3) and those that were judged to be important to both healthcare professional/ researcher and patient/partner stakeholder groups. Nine of outcome domains for which high levels of consensus were reached, were identified through qualitative explorations with survivors of cardiac arrest and their partners. The observed discrepancies between what is reported in cardiac arrest RCTs and what stakeholders view as important may be explained by: which stakeholders are currently involved in selecting assessed outcomes in trials;

the availability of outcome measures; the feasibility of outcome reporting; and the necessity of an outcome domain to specific trials.

Summary of findings from Stage 4: An international consensus meeting

The final stage of the COSCA study was, a 2-day consensus meeting with attendees representing 23 participants from 10 countries including four survivors of cardiac arrest or patient advocates. Participants considered the importance of a short list of 30 outcome domains (16 health across multiple time points) for COS inclusion, this was informed by the results of the modified Delphi survey and initial consensus meeting discussion. The Importance of outcome domains were discussed in small and large group discussions within the core areas of: pathophysiological manifestations (8), survival (5), life impact (15) and economic evaluation and resource impact (2).

During final voting, participants voted for COS inclusion of outcome domains with a Yes or No response, with votes limited up to seven outcome domains for COS inclusions. A high level of consensus (70%) was applied and achieved on three core outcomes domains 1) survival at 30 days/hospital discharge; 2) neurological outcome at 30 days/hospital discharge assessed with the CPC; and 3) health-related quality of life (HRQoL) within the first year.

Participants also explored how to best assess the core outcome domains. Discussions highlighted concerns in the feasibility of outcome assessment

after hospital discharge. It was suggested that functional status (mRS) tools application at hospital discharge may act as a surrogate for the assessment of health related quality of life in the longer term (Nichol et al., 2015).

This research provides a starting point to identifying the concepts of HRQoL that are important to survivors of cardiac arrest, but further work is required to assess the validity and reliability of generic tools and future developed specific tools. When selecting measurement tools it is important to consider the ability to assess emotional and mental wellbeing, social wellbeing and participation, physical function and physical symptoms. Initial discussions informed preliminary recommendation of the consideration of assessment of neurological outcome with the CPC, mRS or GOS-E and HRQoL with the SF-36, the EQ-5D or the HUI-3. Further to this concerns were also raised on the limited evidence of quality and acceptability of methods available to assess the core outcome domains with a need for further work to understand the most appropriate methods to assess core outcome domains.

7.2.3. Implications for outcome reporting in cardiac arrest

The COSCA recommendations provide the first internationally endorsed and multi-stakeholder derived set of guidance for the assessment and reporting of outcomes in future cardiac arrest effectiveness trials. Although intended for different purposes the COSCA recommendations has similarities to the existing guidance for the collection and reporting of registry data - the Utstein Resuscitation Registry template.

Since 1991 the Utstein Resuscitation Registry template has been revised twice. The most recent revision was developed through a number of modified Delphi surveys and consensus meetings of expert healthcare professionals and researchers, however reporting of the methodological details of this process is limited (Cummins et al., 1991, Jacobs et al., 2004, Perkins et al., 2014). The three outcome domains from the COS are reflective of two of the core data elements of the Utstein Resuscitation Registry Template for OHCA: Survival and Neurological outcome at hospital discharge at hospital discharge/ 30days and a supplementary data element: quality of life (Figure 7.1). The COSCA study expands on the Utstein resuscitation registry template providing further guidance on potential measurement tools to assess health related quality of life.

A major difference between the COS and Utstein development was the participation of survivors of cardiac arrest and patient representatives across consensus development. In the future patient contribution as research partners and participants in consensus development methods in Utstein resuscitation template modifications to ensure relevance. Patient involvement is also important to develop Utstein recommendations on assessment of 'Quality of life' and 'patient reported outcome measures; (Perkins et al., 2014).

The similarities between the core outcome set to outcomes reported in the Utstein resuscitation registry template, may aid implementation with familiarity with these outcomes and reducing confusion for trialists.

Although different to COS development, Becker et al have reported with clinical researchers explored whether there is a single primary outcome that should measure across all trials (Becker et al., 2011). The meeting reported by Becker and colleagues concluded that no single outcome should be a primary outcome across trials but the assessment of neurological functional outcome at 90 days with the CPC or mRS is likely to be important to the majority of trials. This differs from the COSCA recommendation neurological outcome assessment at hospital discharge or 30 days. This is frequently measured across trials but may be criticised, providing an initial but inconclusive assessment of patient outcome.

The COSCA study further develops previous guidance (Becker et al., 2011), recommending that neurological outcome assessment at an earlier time point along with survival and HRQoL within 1 year should be reported across all trials as core outcomes (primary or secondary outcomes) across trials supported by votes reaching consensus.

Figure 7.1: Utstein Outcome core and supplementary elements. COSCA
core domains are indicated in bold italics.

Core elements
Survived event
Any ROSC
<i>30 day survival/ survival to hospital discharge</i>
<i>Neurological outcome</i>
Supplementary elements
Transport to hospital
Treatment withdrawal
Cause of death
Organ donation
Patient reported outcome measures
<i>Quality of life measure</i>
12-month survival

7.3. Strengths and contributions of PhD

Many strengths of the methods conducted as part of the COSCA study of have been discussed in the relevant chapters. In this section strengths of the COSCA study and the further contributions to the field of COS development or cardiac arrest research outcome reporting will be discussed. COS development is currently predominantly atheoretical, there is the opportunity for COS development to be theoretically drive in approach. For example, COS developers may consider, the choice of qualitative approaches to identify important outcomes to key stakeholders and the decision making

process in voting for core outcomes. In this chapter strengths and contributions of this thesis are categorised by three of the methodological considerations of COS development: enabling stakeholder participation, identifying and defining outcomes and achieving consensus.

7.3.1. Enabling stakeholder participation

Importance of patient and public involvement

Patient and public involvement (PPI) was a key methodological component of this study. Patients and members of the public were involved as research partners throughout the planning and design stages of the COSCA study. There is currently limited guidance and evidence of patient and public involvement in COS development.

OMERACT have involved patient research partners (PRPs) for some time (de Wit et al., 2011), however reporting the impact of this is limited and has focussed on the role of participants in consensus meetings. In future COS developers involving patients and members of the public as partners should refer to the Guidance for Reporting Involvement of Patients and Public (GRIPP) checklist, to assist describing the process of PPI and its' impact (Staniszewska et al., 2011).

Key areas where PPI support was sought for the COSCA study included: the development of documents and planning of interviews; the structure of the modified Delphi survey; and guidance for the participation of patients at consensus meetings. An example of where PPI had an influence on the

COSCA study was the involvement in the development of the Delphi survey. Through survey piloting with multiple stakeholders including patient partners, it was highlighted that the time point of measurement was important to the scoring of outcome importance. The incorporation of 'when' to assess outcome domains was crucial to patient survey understanding, the importance of 'when' to measure will be discussed further later in this section. Involvement of research partners ensured that the survey was well understood by patient and partner participants. This was reflected in the high number of patients starting and completing the modified Delphi survey (n=69 80%).

The importance of an international contribution

The COSCA study had international representation in both the steering committee and as research participants throughout the consensus development stages. The incorporation of views from an international perspective highlighted differences in care practice and regulation, this was therefore important to working towards and internationally acceptable COS.

At the COSCA consensus meeting a number of discussion points were initiated resulting from the presence of an internationally diverse participant group. Insight from the international and expert contribution obtained from the consensus meeting informed that outcome domain assessment at hospital discharge should be used interchangeably with a measurement at 30 days. However, it is recognised that there may be significant 'time' differences in these two recommendations. Within the final consensus

meeting, there was consideration to the fact that a uniform time point of 30-days would support a consistency in reporting – reflecting the central tenet of a COS; there may be significant variation in the point at which patients are discharged from hospital.

However, significant concerns were raised by international participants that not all healthcare systems could capture survival information post hospital discharge. Therefore, it was agreed that a more ‘flexible’ assessment of survival would be recommended. Moreover, this recommendation is in keeping with the Utstein reporting guidance. This discussion point raises challenges of capturing HRQoL within 1 year as a core outcome domain.

Another example where participation of an international participant group was important, was the discussion of the implications of the implementation of a COS. Concerns were aired that regulatory bodies such as the US Food and Drugs Administration (US FDA), could use this as opportunity to restrict funding to studies. There were concerns that funding bodies would only fund studies reporting COS or restrict funding to the costs associated with core outcomes.

Dissemination of findings will explain the rationale underpinning a COS is to identify the minimum number of outcomes that should be reported across trials across a health area that and made explicit that additional outcomes are reported alongside core outcome domains. The COMET initiative has been endorsed by SPIRIT recommendations, organisations in the UK such as National Institute for Health Research Health Technology Assessment

Programme (<http://www.comet-initiative.org/about/COMETendorsement> cited 18.09.16) and meetings have been attended by international organisations including the US FDA and National (US) Institute for Health (Gargon et al., 2015a), therefore regulatory bodies should be aware of the purpose of core outcome sets.

Despite great efforts capture the most important outcomes to cardiac arrest clinical trials from an international perspective it cannot be certain that outcomes identified were equivalent across cultures. Outcome domains were identified from internationally published studies and qualitative exploration with cardiac arrest survivors and their partners from the UK. To overcome any potential gaps in outcome reporting including those from an international perspective, Delphi survey participants were encouraged to contribute any missing outcome domains.

In consensus development there was participation from a range of nationalities however voting between nationalities was not explored to further understand the importance of outcomes across cultures.

7.3.2. Exploring and defining outcomes

Qualitative exploration with survivors of cardiac arrest and their partners

Qualitative methods to inform COS development have been used infrequently and there limited examples transparently reporting the impact to COS development (Keeley et al., 2016). In this PhD, interviews with cardiac

arrest survivors and their partners enabled a greater understanding of the lived experience and the outcomes that matter to patients. The findings of interviews informed 7 outcome domains (6 health domains at a range of time points) that reached high levels of consensus in both the modified Delphi survey. Outcome domains identified from interviews reached consensus from the perspectives healthcare professionals and researcher and/or and cardiac arrest survivor and partner stakeholder groups.

These findings indicate a single source for identifying potential outcomes for COS inclusion may result in not all important outcome domains being identified. For example, in the COSCA study, many outcome domains identified as important in the modified Delphi would not have been have been identified from a review of outcome reporting in current RCTs alone.

The COSCA study further contributes to the field of COS development, highlighting IPA as a suitable approach to analysis to understand the outcomes that are important to the patient population and in this case of survivors of cardiac arrest. With the complexity of understanding describing and talking about outcomes with patients it was considered that it was most appropriate to understand the lived experience of patients as a whole and from this identify key outcome domains important to patients.

IPA was selected due a commitment to understanding the lived experience of individuals. IPA was previously applied to analyse focus groups with patients with rheumatoid arthritis to better understand outcomes important

from the patients' perspective (Carr et al., 2003). IPA is focussed on the individuals understanding of a phenomenon, this was particularly useful for understanding the sudden unexpected cardiac arrest with variable patient experience and outcome. IPA facilitates the development of an in depth understanding of the individuals' experience, with the researcher immersing themselves in each transcript and completing analysis on an individual case basis, before considering the next participant. This may be particularly useful approach to analysis for other health areas, particularly those in acute health areas.

The importance of when to measure

A major challenge arising from developing a COS for cardiac arrest effectiveness trials was the consideration of when COS development should seek to define 'when' to assess core outcomes. This is an areas of COS development that has received minimal focus, it is clearly stated that 'what' to measure should be identified first, followed by 'how' to measure (Williamson et al., 2012b). There has been vague suggestion that when to measure should be considered whilst addressing how to assess core outcome domains. It is surprising that 'when' to measure outcome domains in a COS hasn't previously been raised as an important consideration. In order to achieve homogeneity and transparency in outcome reporting trialists require instruction of when a core outcome should be assessed.

In the COSCA study the integration of when to measure outcome domains was important, with the meaning and importance of outcome domains

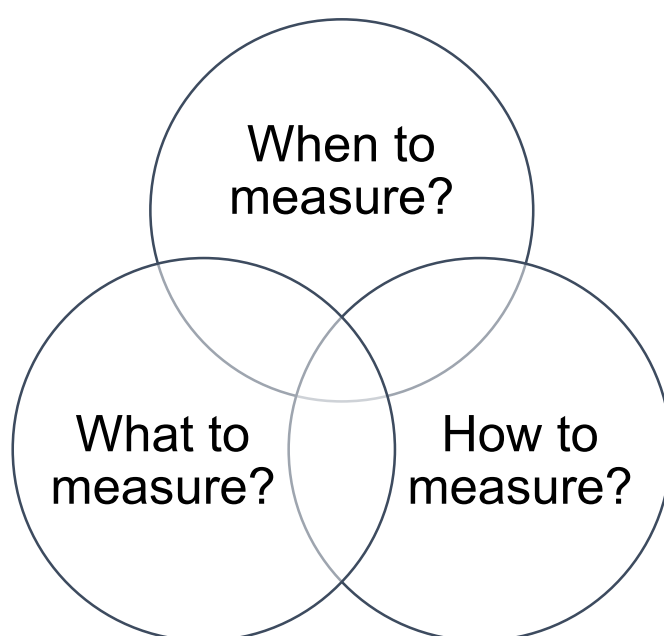
changing over time. During survey piloting with healthcare professionals, researchers and patient and public partners, it was first raised that considering 'when' to measure outcome domains was an important consideration. In addition to this the systematic review of outcomes reported across RCTs, identified a wide range of time point assessment and in interviews patients described their experience and recovery over time.

Piloting raised that the same outcome domain for example, circulatory function could have a different meaning at different time points. Patient partners explained how it was difficult to score the importance of outcome domains as their meaning and importance changed over time. As a result, in the modified Delphi survey outcome domains were listed across the following time points: during CPR; immediately after CPR; during hospital stay; at hospital discharge and within 1 year. The interacting nature of 'what to measure', 'when to measure' and 'how to measure' described is illustrated in figure 7.1.

Few developed Core Outcome Sets have sought to define when outcomes should be measured. In the development of a CDS for maternity care, 263 outcome domains were split into five categories across pregnancy, these were: antenatal, intrapartum, postnatal, foetal/neonatal and additional (Devane et al., 2007). Although similar, this example differs to the COSCA timeframe, with maternity care outcomes listed only having relevant outcome assessment at a single time point.

Further guidance is required for COS developers on how to approach the question of when should core outcomes should be measured, from the conduct and findings of the COSCA study there is the indication that COS developers should consider the time point of measurement at the same time as defining 'what' to measure.

Figure 7.2: Considerations of outcome measurement



7.3.3. Achieving consensus

In this section strengths of the two stage consensus development process will be described. Further to this two major challenges and concerns arose from consensus development, that have not been addressed in depth in the COS literature. These concerns will be described: firstly, the decision making process participants are involved when selecting the most important outcome domains and secondly, the size of a core outcome set.

Consensus development process

A strength of the COSCA study was the rigorous steps taken to achieve consensus on the most important outcome domains to include as part of a COS outcome set, reflective of international and multiple stakeholder views.

COS developed are faced with a number of choices when selecting methods to develop consensus. Other COS developers have used the modified Delphi survey alone to recommend a COS. This could have been an alternative approach for the COSCA study, with the addition of a third round of Delphi asking participants yes or no for inclusion in a core outcome set, allowing a larger contribution of view from an international and multiple stakeholder group.

Although, reflecting on round 2 Delphi survey attrition rates, retention of participants across three rounds of survey would have been a challenge. However, a face to face consensus meeting was chosen due to its advantages in consensus development and decision making. Face to face

processes encourages greater consideration of which outcomes are the most important and areas of uncertainty can be clarified (Jones and Hunter, 1995). Further to this factors contributing to the decision making process and participants voting was highlighted through discussion. Many of these key points would not have been highlighted from the modified Delphi survey without the addition of qualitative questions.

Decision making process

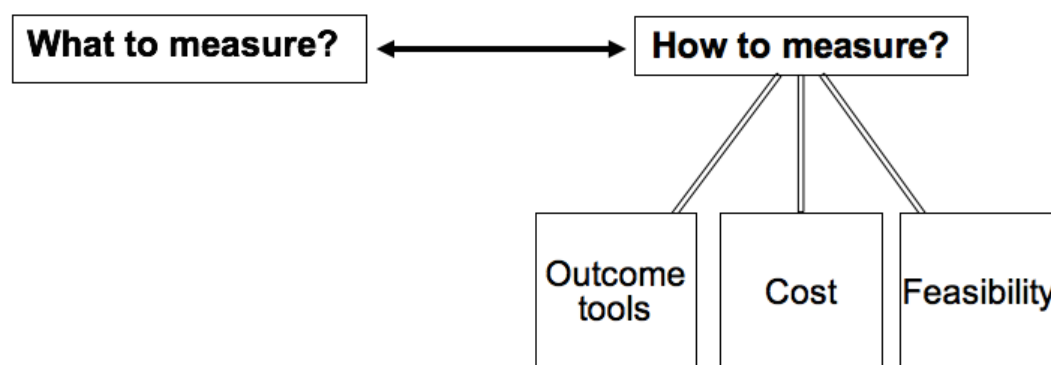
When working towards achieving consensus on the most important outcome domains to include in a COS, participants are faced with a decision making process. This process may be influenced by factors, impacting the participants' responses when asked about the importance of different outcome domains. This concept of consensus development has not previously been explored in Core Outcome Set development. During the COSCA study it was observed that consensus development on the most important outcome domains, 'what' to measure, was influenced by issues surrounding 'how' to measure outcome domains based on the measurement tools available, the feasibility and cost of outcome assessment (Figure 7.3).

Following COS development guidance, the COSCA study sought to identify 'what' to measure followed by 'how' to measure outcome domains. This was emphasised in the modified Delphi survey explaining that the selection measurement tools would be considered once the most important outcome domains had been selected. In the modified Delphi survey, no examples of measurement tools were listed to ensure clarity and that votes weren't

informed by example measurement tools. However, in the COSCA consensus meeting it became clear that participants view on the importance of outcome domains to decision making/ patient recovery was driven by current available measures, the cost and feasibility of measurement.

OMERACT consider the feasibility and qualities of outcome assessment once a CDS has been defined and when considering 'how to measure'(Boers et al., 2015), but the challenge in the COSCA study was the influence of these factors on guiding decisions on what to measure.

Figure 7.3: Decision making selecting important outcome domains



Core Outcome Set size and characteristics

The size of the COS, with three core outcome domains is at the lower limit of COS previously developed. Early examples of core outcome sets developed by the OMERACT group are in the range of 4-8 outcome domains from the field of rheumatology and pain (Bellamy et al., 1997, Turk et al., 2003, Boers et al., 1994, van der Heijde et al., 1997). There is no clear guidance of what is the ideal number for core outcome sets developed and recently larger CDS have been published (Devane et al., 2007, Karas et al., 2014).

Zochling and colleagues describe a seven outcome domain COS for ankylosing spondylitis in patients receiving anti-tumour necrosis factor-alpha therapy, as:

“small enough to be practical, but inclusive enough to manage,”

(Zochling et al., 2008).

Evidence of implementation is only available for a small number of CDS, exploring the uptake of COS in rheumatoid arthritis, ankylosing spondylitis and fall injury prevention (Bautista-Molano et al., 2014, Copsey et al., 2016, Kirkham et al., 2013a). No evidence is available about the implementation of recently published COS, however if a COS is too large there may be challenges with implementation. OMERACT suggest that COS developers should aim for COS no larger than 9 outcome domains (Boers et al., 2015), acknowledging that Cochrane Summary findings tables allow the input of up

to 7 outcomes and stressing that COS aim to capture the minimum number of domains to answer research questions.

OMERACT have recently recommended that a core outcome set should include an outcome domain from each of the core areas: pathophysiological manifestations, survival/death and life impact (Boers et al., 2014b). In the COSCA study outcome domains were not identified as core and appropriate for cardiac arrest effectiveness trials, from the core area pathophysiological manifestations due to the variable nature of interventions. In addition to this, this recommendation from OMERACT is influenced by how researchers choose to classify outcome domains with some not limited to one core area, OMERACT acknowledge there maybe overlap between core areas(Boers et al., 2014a).

For example, the COSCA study group classified neurological outcome as a life impact measure rather than a measure of pathological manifestations, due to the frequent assessment with the use of objective scales detailing symptoms that have an impact on patients' day to day life. This was in contrast to other biological markers of neurological function such as NSE and S100B which were classified as brain function, within the core area pathophysiological manifestations.

7.4. Limitations of PhD

Limitations of specific methods have been discussed within each chapter.

Some broader limitations of the COSCA study are discussed.

7.4.1. Methodological challenges

In COS development researchers are faced with many different choices influence the success of the process. Specific methodological challenges have been discussed within relevant chapters.

A limitation of this study was that the methods were conducted by the lead researcher, supported by the guidance of the steering group with a wide range of expertise. Core outcome sets are often developed by a multidisciplinary team allowing for rapid development and increased rigour. This study was aided by the contribution from the expert steering group however, a team approach to the outcome framework development for consensus methods could have been adopted. Due to the complexity of measurement and terminology alterations were made between outcome classification between methods. These challenges were highlighted in the COSCA consensus meeting when considering 'neurological outcome'. However, the adapted nature of the face to face meeting allowed the incorporation of wider expert views.

7.4.2. Representation of stakeholder views

Firstly, a limitation of the study was the conduct in the English language only. Due to logistical and ethical implications face to face interviews were conducted with a small group of patients admitted to a large NHS trust in the Midlands (UK). It is important to acknowledge that patient experience of care and recovery is likely to be different regionally and internationally reflecting cultural and healthcare system differences. The modified Delphi survey broadened patient views internationally but this was dominated by English speaking countries as it was a requirement that participants had sufficient understanding of English in order to complete the survey. Although patient participation was dominated by English speaking countries, there was a mix between the UK, North America and Australia, representing the views of participants from diverse healthcare systems.

Further to this, despite the COSCA capturing the view of multiple stakeholders including: healthcare professionals with a diversity of experience; research from varied areas of expertise; cardiac arrest survivors and partners, a number of key stakeholders did not participate in the development of this COS.

Recent guidance from OMERACT suggest the following stakeholders should be considered in COS development: researchers; clinicians; funders; government regulatory authorities; healthcare policy groups; trial managers; patients and consumers; family and care givers; advocacy groups and payers (Boers et al., 2015). The full list was published after the inception of

the COSCA study however there is evidence of industry representatives, health economists and journal editors participating in COS development in the past (Schmitt et al., 2012, Bartlett et al., 2012). On reflection recruitment of such stakeholders should have been targeted. However, a number of the healthcare professionals and researchers participating in the consensus development methods have multiple stakeholder roles within the field of resuscitation research. For example, clinical researchers may have roles on funding panels, healthcare management, journal editors and play a role in developing clinical guidelines. Acknowledgement of this variety of contribution was limited by the demographic questions asked in the modified Delphi survey, comment box or the option of multiple responses would have been beneficial. As a result, 11.6% participants selected themselves as “other” from physicians, allied health professionals, nurses, academics and other.

Although, patient and public participants contributed to methods to identify outcome domains and consensus on the most important domains, we cannot be certain that the core outcome set captures all the outcomes that are the most important to survivors of cardiac arrest. In the modified Delphi survey it was a strength to keep groups separately to understand differences in score preference. However, this produced an extensive list that was taken forward to the consensus meeting. A different approach to questioning may have identified the very most important outcomes to a larger patient and public participant group.

At the meeting there were 4 patient and public representatives in addition to the 19 healthcare professionals and researchers. Each group had a patient and public representative to remind participants to consider outcomes that are important to all stakeholders of cardiac arrest trials including patients. Quantification of stakeholder differences was possible but should be taken with caution due to the difference in participant number (4:19). All core domains included votes from patient and public representatives.

With a high consensus level of 70% a vote of yes for COS inclusion, consensus could have been achieved on the views of the healthcare professional and researcher group alone but not the patient and public stakeholder group. To overcome such challenges votes could have been weighted between stakeholder groups.

7.5. Future research and dissemination

Core outcome measurement set development

Research presented is the initial stage of core outcome set development with further research required to define a full COS. The results of the COSCA have defined a core domain set, defining 'what' outcomes should be measured as part of a core outcome set. Broad time points of assessment were defined for the CDS and specific time points for two of the three core outcomes, further consensus development is required to define a time point of when HRQoL should be assessed.

Further to the development of a CDS a core outcome measurement set should be defined, explaining the outcome measurement tools that should be the suitability of potential measurement tools to assess neurological outcome (at hospital discharge/30days) and health related quality of life (within the first year). Defining how to measure is required to ensure that there is homogeneity in outcome reporting across trials. Although initial recommendations of how to assess core outcome domains based on expert experience and discussion, a further review of the quality and acceptability of potential available outcome measurement tools is required.

Dissemination of research findings

Dissemination of the different sub-studies: systematic review, interviews with patients, an international modified Delphi survey and an international consensus meeting have been presented at a variety of conferences: Royal College of Nursing Research conference, European Resuscitation Council Congress, COMET meetings and in both poster and oral presentations by members of the lead study team. The findings of the COSCA consensus meeting concluding the study were presented immediately after at the ERC Congress in Prague, to large audiences that will be conducting studies using the COS.

Interview participants will receive an evidence synthesis, developed with the assistance of patient partners of the CRAG group to explain the findings of the interviews and contribution to the overall study. Participants of the Delphi survey answered a question to whether they wanted to hear more about the

study results upon publication. Healthcare professionals and researcher participants will receive an email with a copy of the publication findings attached. A summary of findings developed with patient partners from the CRAG group will be circulated to patient and partner participants.

The systematic review (chapter 1) has been published in *Resuscitation Journal* (Whitehead et al., 2015). Plans are in place to publish the findings of the qualitative interviews with patients and their partners, a protocol paper detailing the methodological considerations throughout the COSCA study and a summary paper of the COSCA study including key findings from the modified Delphi survey and international consensus meeting.

Core Outcome Set Implementation

Guidance on how to ensure successful implementation and uptake of a COS is not available. After reviewing the implementation of a COS in fall prevention authors identified considerations to aid implementation (Copsey et al., 2016). For example, the importance of a range of academic and geographic by in is important to promote implementation with participants taking responsibility and ownership. In addition to this a dissemination strategy and evaluation of impact was raised as important.

In addition to the dissemination activities described, the COSCA study sought relationships and endorsement from organisations within the field of cardiac arrest to increase awareness and recognition of the importance of COS development and implementation. The COSCA study has received

endorsement from ILCOR and the ERC and has representatives from these organisations as participants within the studies.

There is a need to further understanding the success of COS and need for guidance on approaches to enable successful implementation to ensure that the benefits of COS are seen and research is not wasted. It also is recommended that COS are reviewed and updated (OMERACT handbook) (Boers et al., 2015) to reflect advances within a healthcare area, this will be a consideration for the future of the core outcome set for cardiac arrest effectiveness trials. Alongside reviewing the contents of the COS it important to assess the success of implementation and impact of the COS.

7.6. Implications of research findings

This PhD highlights the great heterogeneity in outcome reporting across cardiac arrest, indicating the need for standardisation to increase the comparability and value of future research in this field. Currently there is great variation in which outcomes are measured, how they are measured and the time point of measurement. A lack in transparent reporting of how outcomes are defined was also highlighted. The findings indicate need to improve the state of outcome reporting in this field.

This is the first to explore the lived experience of survivors of CA and their partners, specifically focussed on seeking to better understand how their life post-survival is affected and how they determine what really matters in terms

of a 'good outcome'. It is evident that the journey post-survival is a long one, and that seeking to better understand what really matters to patients post hospital discharge is crucial to informing the appropriate provision of care and support for survivors and their partners.

Failure to seek to understand the patients' perspective – and the historic reliance on the perspective of the clinicians suggests that healthcare is currently not responding to the longer-term needs of this group. There is the need for the incorporation of well-developed, patient-derived measures of HRQoL in the long-term follow-up of patients could assist in the signposting of healthcare services for this population.

7.7. Thesis conclusions

This thesis contributes a significant area of research to both the field of core outcome set development and cardiac arrest research.

Core outcome set development has progressed significantly over the last 20-years, with a recent shift towards the greater engagement with both patients and representatives from multiple health-related disciplines who may need to engage with the results from clinical trials. This thesis reports: the value of qualitative research in identifying outcomes important to patients and the application of patient and public involvement.

Further to this, this thesis identified COS additional key methodological considerations for future COS developers. A major contribution was highlighting the importance of defining “when” core outcomes should be measured. Time point of measurement has not previously been a focus of COS development but is an important factor determining ‘what’ is being measured and influences homogeneity in outcome reporting. An additional methodological consideration identified was the need for consideration of the decision making process influencing core outcome set inclusion.

A review of outcome reporting in cardiac arrest research highlighted the strong focus on clinician-derived outcomes, with a limited attempt to understand survival from the perspective of the survivor. This research was the first to seek to understand the meaning of survival and the outcomes that really matter to survivors of cardiac arrest and their partners. This research was also the first to seek to understand the outcomes judged to be important by an international, multi-stakeholder group and that should be considered, as a minimum, for inclusion in future effectiveness trials of cardiac arrest.

These findings highlighted the significant discrepancies between what is currently assessed in published cardiac arrest research, and those outcomes judged to be important by clinicians, health professionals, researchers, survivors and their partners. A final consensus meeting of multiple stakeholders further explored the relevance and importance of a short-list of outcome domains and potential measurement approaches to arrive at a

consensus recommendation for a core outcome set for cardiac arrest effectiveness trials.

The COSCA recommendation, a minimum of three core outcome domains: survival to hospital discharge/30days, neurological outcome at hospital discharge/30 days and HRQoL within 1 year. The COS is grounded in the views of survivors of cardiac arrest, their partners, clinicians, health professionals and researchers from an international setting. It is currently recommended for application in future CA effectiveness trials. Further research is required to ratify the selection of outcome measures and to ensure that there is consistency in the way in which the outcome domains are assessed.

This thesis contributes to the fields of both Cardiac Arrest and COS development research, and following further refinement of the selection of outcome measures, will enhance the relevance and consistency in the way in which outcomes are assessed in clinical research.

The key finding of this thesis is that outcome reporting in cardiac arrest is currently heterogeneous limiting comparability of findings and fails to capture the outcomes that are the most important to a range of key stakeholders.

Bibliography

- Ajam, K., Gold, L. S., Beck, S. S., Damon, S., Phelps, R. and Rea, T. D. (2011) 'Reliability of the Cerebral Performance Category to classify neurological status among survivors of ventricular fibrillation arrest: a cohort study', *Scand J Trauma Resusc Emerg Med*, 19, pp. 38.
- Andrade, C. (2015) 'The primary outcome measure and its importance in clinical trials', *J Clin Psychiatry*, 76(10), pp. e1320-3.
- Andrew, E., Nehme, Z., Bernard, S. and Smith, K. (2016) 'Comparison of health-related quality of life and functional recovery measurement tools in out-of-hospital cardiac arrest survivors', *Resuscitation*, 107, pp. 57-64.
- Appleby, J., Devlin, N., Maynard, A., Scott, H. and Vallance-Owen, A. (2004) 'Measuring success in the NHS', *London: Dr Foster, Kings Fund and City University*.
- Arrich, J., Holzer, M., Havel, C., Müllner, M. and Herkner, H. (2016) 'Hypothermia for neuroprotection in adults after cardiopulmonary resuscitation', *Cochrane Database Syst Rev*, 2, pp. CD004128.
- Arroll, M. A. and Senior, V. (2008) 'Individuals' experience of chronic fatigue syndrome/myalgic encephalomyelitis: An interpretative phenomenological analysis', *Psychology and Health*, 23(4), pp. 443-458.
- Arts, D. G., De Keizer, N. F. and Scheffer, G. J. (2002) 'Defining and improving data quality in medical registries: a literature review, case study, and generic framework', *J Am Med Inform Assoc*, 9(6), pp. 600-11.
- Atwood, C., Eisenberg, M. S., Herlitz, J. and Rea, T. D. (2005) 'Incidence of EMS-treated out-of-hospital cardiac arrest in Europe', *Resuscitation*, 67(1), pp. 75-80.
- Aufderheide, T. P., Pirrallo, R. G., Provo, T. A. and Lurie, K. G. (2005) 'Clinical evaluation of an inspiratory impedance threshold device during standard cardiopulmonary resuscitation in patients with out-of-hospital cardiac arrest', *Critical Care Medicine*, 33(4), pp. 734-40.
- Aung, K. and Htay, T. (2005) 'Vasopressin for cardiac arrest: a systematic review and meta-analysis', *Arch Intern Med*, 165(1), pp. 17-24.
- Bagley, H., Young, B. and Williamson, P. R. (2015) 'The Patient and Public Involvement Activities of the COMET Initiative', *Trials*, 16(3), pp. 1-1.
- Bartlett, S. J., Bykerk, V. P., Cooksey, R., Choy, E. H., Alten, R., Christensen, R., Furst, D. E., Guillemin, F., Halls, S., Hewlett, S., Leong, A. L., Lyddiatt, A., March, L., Montie, P., Orbai, A. M., Pohl, C., Scholte Voshaar, M., Woodworth, T. G. and Bingham, C. O. (2015) 'Feasibility and Domain Validation of Rheumatoid Arthritis (RA) Flare Core Domain Set: Report of the OMERACT 2014 RA Flare Group Plenary', *J Rheumatol*.
- Bartlett, S. J., Hewlett, S., Bingham, C. O., Woodworth, T. G., Alten, R., Pohl, C., Choy, E. H., Sanderson, T., Boonen, A., Bykerk, V., Leong, A. L., Strand, V., Furst, D. E., Christensen, R. and Group, O. R. F. W. (2012) 'Identifying core domains to assess flare in rheumatoid arthritis:

- an OMERACT international patient and provider combined Delphi consensus', *Ann Rheum Dis*, 71(11), pp. 1855-60.
- Bautista-Molano, W., Navarro-Compán, V., Landewé, R. B., Boers, M., Kirkham, J. J. and van der Heijde, D. (2014) 'How well are the ASAS/OMERACT Core Outcome Sets for Ankylosing Spondylitis implemented in randomized clinical trials? A systematic literature review', *Clin Rheumatol*, 33(9), pp. 1313-22.
- Becker, L. B., Aufderheide, T. P., Geocadin, R. G., Callaway, C. W., Lazar, R. M., Donnino, M. W., Nadkarni, V. M., Abella, B. S., Adrie, C., Berg, R. A., Merchant, R. M., O'Connor, R. E., Meltzer, D. O., Holm, M. B., Longstreth, W. T., Halperin, H. R., Committee, A. H. A. E. C. C. and Council on Cardiopulmonary, C. C., Perioperative and Resuscitation (2011) 'Primary outcomes for resuscitation science studies: a consensus statement from the American Heart Association', *Circulation*, 124(19), pp. 2158-77.
- Becker, L. B., Smith, D. W. and Rhodes, K. V. (1993) 'Incidence of cardiac arrest: a neglected factor in evaluating survival rates', *Ann Emerg Med*, 22(1), pp. 86-91.
- Beesems, S. G., Wittebrood, K. M., de Haan, R. J. and Koster, R. W. (2014) 'Cognitive function and quality of life after successful resuscitation from cardiac arrest', *Resuscitation*, 85(9), pp. 1269-74.
- Bellamy, N., Kirwan, J., Boers, M., Brooks, P., Strand, V., Tugwell, P., Altman, R., Brandt, K., Dougados, M. and Lequesne, M. (1997) 'Recommendations for a core set of outcome measures for future phase III clinical trials in knee, hip, and hand osteoarthritis. Consensus development at OMERACT III', *J Rheumatol*, 24(4), pp. 799-802.
- Berdowski, J., Berg, R. A., Tijssen, J. G. and Koster, R. W. (2010) 'Global incidences of out-of-hospital cardiac arrest and survival rates: Systematic review of 67 prospective studies', *Resuscitation*, 81(11), pp. 1479-87.
- Bergner, M. (1985) 'Measurement of health status', *Med Care*, 23(5), pp. 696-704.
- Biggerstaff, D. (2012) *Qualitative research methods in psychology*. InTech.
- Biggerstaff, D. and Thompson, A. R. (2008) 'Interpretative phenomenological analysis (IPA): A qualitative methodology of choice in healthcare research', *Qualitative Research in Psychology*, 5(3), pp. 214-224.
- Black, N. (2007) 'Consensus development methods', *Qualitative Research in Health Care, Third Edition*, pp. 132-141.
- Black, N. (2013) 'Patient reported outcome measures could help transform healthcare', *BMJ*, 346, pp. f167.
- Black, N., Murphy, M., Lamping, D., McKee, M., Sanderson, C., Askham, J. and Marteau, T. (1999) 'Consensus development methods: a review of best practice in creating clinical guidelines', *J Health Serv Res Policy*, 4(4), pp. 236-48.
- Blencowe, N. S., Strong, S., McNair, A. G., Brookes, S. T., Crosby, T., Griffin, S. M. and Blazeby, J. M. (2012) 'Reporting of short-term clinical outcomes after esophagectomy: a systematic review', *Ann Surg*, 255(4), pp. 658-66.

- Boers, M., Idzerda, L., Kirwan, J. R., Beaton, D., Escorpizo, R., Boonen, A., Magasi, S., Sinha, I., Stucki, G. and Tugwell, P. (2014a) 'Toward a generalized framework of core measurement areas in clinical trials: a position paper for OMERACT 11', *J Rheumatol*, 41(5), pp. 978-85.
- Boers, M., Kirwan, J. R., Gossec, L., Conaghan, P. G., D'Agostino, M. A., Bingham, C. O., Brooks, P. M., Landewé, R., March, L., Simon, L., Singh, J. A., Strand, V., Wells, G. A. and Tugwell, P. (2014b) 'How to choose core outcome measurement sets for clinical trials: OMERACT 11 approves filter 2.0', *J Rheumatol*, 41(5), pp. 1025-30.
- Boers, M., Kirwan, J. R., Tugwell, P. and al, e. 2015. The OMERACT Handbook. Published by OMERACT.
- Boers, M., Kirwan, J. R., Wells, G., Beaton, D., Gossec, L., d'Agostino, M. A., Conaghan, P. G., Bingham, C. O., Brooks, P., Landewé, R., March, L., Simon, L. S., Singh, J. A., Strand, V. and Tugwell, P. (2014c) 'Developing Core Outcome Measurement Sets for Clinical Trials: OMERACT Filter 2.0', *J Clin Epidemiol*.
- Boers, M., Tugwell, P., Felson, D. T., van Riel, P. L., Kirwan, J. R., Edmonds, J. P., Smolen, J. S., Khaltsev, N. and Muirden, K. D. (1994) 'World Health Organization and International League of Associations for Rheumatology core endpoints for symptom modifying antirheumatic drugs in rheumatoid arthritis clinical trials', *J Rheumatol Suppl*, 41, pp. 86-9.
- Bombardier, C., Tugwell, P., Sinclair, A., Dok, C., Anderson, G. and Buchanan, W. (1982) 'Preference for endpoint measures in clinical trials: results of structured workshops', *The Journal of rheumatology*, 9(5), pp. 798.
- Bonita, R. and Beaglehole, R. (1988) 'Modification of Rankin Scale: Recovery of motor function after stroke', *Stroke*, Dec 19((12)), pp. 1497-1500.
- Borkoles, E., Nicholls, A. R., Bell, K., Butterly, R. and Polman, R. C. (2008) 'The lived experiences of people diagnosed with multiple sclerosis in relation to exercise', *Psychol Health*, 23(4), pp. 427-41.
- Bossaert, L. L., Perkins, G. D., Askitopoulou, H., Raffay, V. I., Greif, R., Haywood, K. L., Mentzelopoulos, S. D., Nolan, J. P., Van de Voorde, P., Xanthos, T. T. and Collaborators, e. o. r. a. e.-o.-l. d. s. (2015) 'European Resuscitation Council Guidelines for Resuscitation 2015: Section 11. The ethics of resuscitation and end-of-life decisions', *Resuscitation*, 95, pp. 302-11.
- Bowling, A. (2005) *Measuring health : a review of quality of life measurement scales*. 3rd edn. Maidenhead, Berkshire, England ; New York, NY: Open University Press.
- Bowling, A. (2014) *Research methods in health: investigating health and health services*. McGraw-Hill Education (UK).
- Braun, V. and Clarke, V. (2006) 'Using thematic analysis in psychology', *Qualitative research in psychology*, 3(2), pp. 77-101.
- Breil, M., Krep, H., Heister, U., Bartsch, A., Bender, R., Schaefer, B., Hoeft, A. and Fischer, M. (2012) 'Randomised study of hypertonic saline infusion during resuscitation from out-of-hospital cardiac arrest', *Resuscitation*, 83(3), pp. 347-52.

- Bremer, A., Dahlberg, K. and Sandman, L. (2009a) 'Experiencing out-of-hospital cardiac arrest: significant others' lifeworld perspective', *Qual Health Res*, 19(10), pp. 1407-20.
- Bremer, A., Dahlberg, K. and Sandman, L. (2009b) 'To survive out-of-hospital cardiac arrest: a search for meaning and coherence', *Qual Health Res*, 19(3), pp. 323-38.
- Breslow, L. (2006) 'Health measurement in the third era of health', *Am J Public Health*, 96(1), pp. 17-9.
- Brocki, J. M. and Wearden, A. J. (2006) 'A critical evaluation of the use of interpretative phenomenological analysis (IPA) in health psychology', *Psychology and health*, 21(1), pp. 87-108.
- Brundage, M., Bass, B., Davidson, J., Queenan, J., Bezjak, A., Ringash, J., Wilkinson, A. and Feldman-Stewart, D. (2011) 'Patterns of reporting health-related quality of life outcomes in randomized clinical trials: implications for clinicians and quality of life researchers', *Qual Life Res*, 20(5), pp. 653-64.
- Burton, A. E., Shaw, R. L. and Gibson, J. M. (2013) 'Living together with age-related macular degeneration: An interpretative phenomenological analysis of sense-making within a dyadic relationship', *J Health Psychol.*
- Bury, M. (1982) 'Chronic illness as biographical disruption', *Sociol Health Illn*, 4(2), pp. 167-82.
- Calderon, L. M., Guyette, F. X., Doshi, A. A., Callaway, C. W., Rittenberger, J. C. and Service, P. C. A. (2014) 'Combining NSE and S100B with clinical examination findings to predict survival after resuscitation from cardiac arrest', *Resuscitation*, 85(8), pp. 1025-9.
- Calvert, M., Brundage, M., Jacobsen, P. B., Schünemann, H. J. and Efficace, F. (2013) 'The CONSORT Patient-Reported Outcome (PRO) extension: implications for clinical trials and practice', *Health and quality of life outcomes*, 11(1), pp. 184.
- Carr, A., Hewlett, S., Hughes, R., Mitchell, H., Ryan, S., Carr, M. and Kirwan, J. (2003) 'Rheumatology outcomes: the patient's perspective', *The Journal of rheumatology*, 30(4), pp. 880-883.
- Cella, D., Yount, S., Rothrock, N., Gershon, R., Cook, K., Reeve, B., Ader, D., Fries, J. F., Bruce, B., Rose, M. and Group, P. C. (2007) 'The Patient-Reported Outcomes Measurement Information System (PROMIS): progress of an NIH Roadmap cooperative group during its first two years', *Med Care*, 45(5 Suppl 1), pp. S3-S11.
- Cerchiari, E. L. (2007) 'Postresuscitation syndrome', in Paradis, N.A., Halperin, H.R., Kern, K.B., Wenzel, V. & Chamberlain, D.A. (eds.) *Cardiac Arrest: The Science and Practice of Resuscitation Medicine*: Cambridge University Press, pp. 817-828.
- Chalder, T., Berelowitz, G., Pawlikowska, T., Watts, L., Wessely, S., Wright, D. and Wallace, E. P. (1993) 'Development of a fatigue scale', *J Psychosom Res*, 37(2), pp. 147-53.
- Chalmers, I., Bracken, M. B., Djulbegovic, B., Garattini, S., Grant, J., Gülmezoglu, A. M., Howells, D. W., Ioannidis, J. P. and Oliver, S. (2014) 'How to increase value and reduce waste when research priorities are set', *Lancet*, 383(9912), pp. 156-65.

- Chalmers, I. and Glasziou, P. (2009) 'Avoidable waste in the production and reporting of research evidence', *Lancet*, 374(9683), pp. 86-9.
- Chan, A. W., Tetzlaff, J. M., Gøtzsche, P. C., Altman, D. G., Mann, H., Berlin, J. A., Dickersin, K., Hróbjartsson, A., Schulz, K. F., Parulekar, W. R., Krleza-Jeric, K., Laupacis, A. and Moher, D. (2013) 'SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials', *BMJ*, 346, pp. e7586.
- Chapman, E., Parameshwar, J., Jenkins, D., Large, S. and Tsui, S. (2007) 'Psychosocial issues for patients with ventricular assist devices: a qualitative pilot study', *Am J Crit Care*, 16(1), pp. 72-81.
- Choices, N. (2008) 'About the NHS', *NHS Choices*.
- Clarke, L., Clarke, M. and Clarke, T. (2007) 'How useful are Cochrane reviews in identifying research needs?', *J Health Serv Res Policy*, 12(2), pp. 101-3.
- Clarke, M. (2007) 'Standardising outcomes for clinical trials and systematic reviews', *Trials*, 8, pp. 39.
- Clarke, M. and Williamson, P. (2015) 'Core outcome sets and trial registries', *Trials*, 16, pp. 216.
- Cobb, L. A. (2007) 'Sequence of therapies during resuscitation: application of CPR', in Paradis, N.A., Halperin, H.R., Kern, K.B., Wenzel, V. & Chamberlain, D.A. (eds.) *Cardiac Arrest: The Science and Practice of Resuscitation Medicine*: Cambridge University Press, pp. 463-469.
- Copsey, B., Hopewell, S., Becker, C., Cameron, I. D. and Lamb, S. E. (2016) 'Appraising the uptake and use of recommendations for a common outcome data set for clinical trials: a case study in fall injury prevention', *Trials*, 17(1), pp. 131.
- Cronberg, T., Lilja, G., Horn, J., Kjaergaard, J., Wise, M. P., Pellis, T., Hovdenes, J., Gasche, Y., Åneman, A., Stammet, P., Erlinge, D., Friberg, H., Hassager, C., Kuiper, M., Wanscher, M., Bosch, F., Cranshaw, J., Kleger, G. R., Persson, S., Undén, J., Walden, A., Winkel, P., Wetterslev, J., Nielsen, N. and Investigators, T. T. (2015) 'Neurologic Function and Health-Related Quality of Life in Patients Following Targeted Temperature Management at 33°C vs 36°C After Out-of-Hospital Cardiac Arrest: A Randomized Clinical Trial', *JAMA Neurol*, 72(6), pp. 634-41.
- Crowe, S., Fenton, M., Hall, M., Cowan, K. and Chalmers, I. (2015) 'Patients', clinicians' and the research communities' priorities for treatment research: there is an important mismatch', *Research Involvement and Engagement*, 1(1), pp. 2.
- Cummins, R. O., Chamberlain, D. A., Abramson, N. S., Allen, M., Baskett, P. J., Becker, L., Bossaert, L., Delooz, H. H., Dick, W. F. and Eisenberg, M. S. (1991) 'Recommended guidelines for uniform reporting of data from out-of-hospital cardiac arrest: the Utstein Style. A statement for health professionals from a task force of the American Heart Association, the European Resuscitation Council, the Heart and Stroke Foundation of Canada, and the Australian Resuscitation Council', *Circulation*, 84(2), pp. 960-75.
- Dalkey, N. and Helmer, O. (1963) 'An experimental application of the Delphi method to the use of experts', *Management science*, 9(3), pp. 458-467.

- Davies, H. T. and Crombie, I. K. (1997) 'Interpreting health outcomes', *J Eval Clin Pract*, 3(3), pp. 187-99.
- Dawson, J., Fitzpatrick, R., Carr, A. and Murray, D. (1996) 'Questionnaire on the perceptions of patients about total hip replacement', *J Bone Joint Surg Br*, 78(2), pp. 185-90.
- de Wit, M., Abma, T., Koelewijn-Van Loon, M., Collins, S. and Kirwan, J. (2013a) 'Facilitating and inhibiting factors for long-term involvement of patients at outcome conferences--lessons learnt from a decade of collaboration in OMERACT: a qualitative study', *BMJ Open*, 3(8), pp. e003311.
- de Wit, M., Abma, T., Koelewijn-van Loon, M., Collins, S. and Kirwan, J. (2013b) 'Involving patient research partners has a significant impact on outcomes research: a responsive evaluation of the international OMERACT conferences', *BMJ Open*, 3(5).
- de Wit, M. P., Abma, T. A., Koelewijn-van Loon, M. S., Collins, S. and Kirwan, J. (2014) 'What has been the effect on trial outcome assessments of a decade of patient participation in OMERACT?', *J Rheumatol*, 41(1), pp. 177-84.
- de Wit, M. P., Berlo, S. E., Aanerud, G. J., Aletaha, D., Bijlsma, J. W., Croucher, L., Da Silva, J. A., Glüsing, B., Gossec, L., Hewlett, S., Jongkees, M., Magnusson, D., Scholte-Voshaar, M., Richards, P., Ziegler, C. and Abma, T. A. (2011) 'European League Against Rheumatism recommendations for the inclusion of patient representatives in scientific projects', *Ann Rheum Dis*, 70(5), pp. 722-6.
- de Wit, M. P., Koelewijn-van Loon, M. S., Collins, S., Abma, T. A. and Kirwan, J. (2013c) "'If I wasn't this robust": Patients' expectations and experiences at the Outcome Measures in Rheumatology Conference 2010', *The Patient-Patient-Centered Outcomes Research*, 6(3), pp. 179-187.
- DeAngelis, C. D., Drazen, J. M., Frizelle, F. A., Haug, C., Hoey, J., Horton, R., Kotzin, S., Laine, C., Marusic, A., Overbeke, A. J., Schroeder, T. V., Sox, H. C., Van Der Weyden, M. B. and Editors, I. C. o. M. J. (2004) 'Clinical trial registration: a statement from the International Committee of Medical Journal Editors', *JAMA*, 292(11), pp. 1363-4.
- Delbecq, A. L. and Van de Ven, A. H. (1971) 'A group process model for problem identification and program planning', *The Journal of Applied Behavioral Science*, 7(4), pp. 466-492.
- Devane, D., Begley, C. M., Clarke, M., Horey, D. and OBoyle, C. (2007) 'Evaluating maternity care: a core set of outcome measures', *Birth*, 34(2), pp. 164-72.
- Dicicco-Bloom, B. and Crabtree, B. F. (2006) 'The qualitative research interview', *Med Educ*, 40(4), pp. 314-21.
- Dickersin, K. (1990) 'The existence of publication bias and risk factors for its occurrence', *JAMA*, 263(10), pp. 1385-9.
- Dickersin, K. and Min, Y. I. (1993) 'NIH clinical trials and publication bias', *Online J Curr Clin Trials*, Doc No 50, pp. [4967 words; 53 paragraphs].
- Distler, O., Behrens, F., Pittrow, D., Huscher, D., Denton, C. P., Foeldvari, I., Humbert, M., Matucci-Cerinic, M., Nash, P., Opitz, C. F., Rubin, L. J., Seibold, J. R., Furst, D. E. and Group, E.-O. (2008) 'Defining

- appropriate outcome measures in pulmonary arterial hypertension related to systemic sclerosis: a Delphi consensus study with cluster analysis', *Arthritis Rheum*, 59(6), pp. 867-75.
- Dixon-Woods, M. (2011) 'Using framework-based synthesis for conducting reviews of qualitative studies', *BMC Med*, 9, pp. 39.
- Dorman, P. J., Waddell, F., Slattery, J., Dennis, M. and Sandercock, P. (1997) 'Are proxy assessments of health status after stroke with the EuroQol questionnaire feasible, accurate, and unbiased?', *Stroke*, 28(10), pp. 1883-7.
- Dougherty, C. M. (1994) 'Longitudinal recovery following sudden cardiac arrest and internal cardioverter defibrillator implantation: survivors and their families', *Am J Crit Care*, 3(2), pp. 145-54.
- Dougherty, C. M., Benoliel, J. Q. and Bellin, C. (2000) 'Domains of nursing intervention after sudden cardiac arrest and automatic internal cardioverter defibrillator implantation', *Heart Lung*, 29(2), pp. 79-86.
- Douglas, R. S., Tsirbas, A., Gordon, M., Lee, D., Khadavi, N., Garneau, H. C., Goldberg, R. A., Cahill, K., Dolman, P. J., Elner, V., Feldon, S., Lucarelli, M., Uddin, J., Kazim, M., Smith, T. J., Khanna, D. and Society, I. T. E. D. (2009) 'Development of criteria for evaluating clinical response in thyroid eye disease using a modified Delphi technique', *Arch Ophthalmol*, 127(9), pp. 1155-60.
- Duncan, P. W., Jorgensen, H. S. and Wade, D. T. (2000) 'Outcome measures in acute stroke trials: a systematic review and some recommendations to improve practice', *Stroke*, 31(6), pp. 1429-38.
- Dwan, K., Altman, D. G., Arnaiz, J. A., Bloom, J., Chan, A. W., Cronin, E., Decullier, E., Easterbrook, P. J., Von Elm, E., Gamble, C., Gherzi, D., Ioannidis, J. P., Simes, J. and Williamson, P. R. (2008) 'Systematic review of the empirical evidence of study publication bias and outcome reporting bias', *PLoS One*, 3(8), pp. e3081.
- Easterbrook, P. J., Berlin, J. A., Gopalan, R. and Matthews, D. R. (1991) 'Publication bias in clinical research', *Lancet*, 337(8746), pp. 867-72.
- Eatough, V. and Smith, J. A. (2008) 'Interpretative Phenomenological Analysis', in *The SAGE handbook of qualitative research in psychology*. pp. pages 179-194 [Online]. Version. Available at: <http://methods.sagepub.com/book/the-sage-handbook-of-qualitative-research-in-psychology>.
- Egger, M., Smith, G. D. and Phillips, A. N. (1997) 'Meta-analysis: principles and procedures', *BMJ*, 315(7121), pp. 1533-7.
- Einav, S., Kaufman, N., Algur, N. and Kark, J. D. (2012) 'Modeling serum biomarkers S100 beta and neuron-specific enolase as predictors of outcome after out-of-hospital cardiac arrest: an aid to clinical decision making', *J Am Coll Cardiol*, 60(4), pp. 304-11.
- Eleftheriadou, V., Thomas, K., van Geel, N., Hamzavi, I., Lim, H., Suzuki, T., Katayama, I., Anbar, T., Abdallah, M., Benzekri, L., Gauthier, Y., Harris, J., Silva de Castro, C. C., Pandya, A., Goh, B. K., Lan, C. C., Oiso, N., Al Issa, A., Esmat, S., Le Poole, C., Lee, A. Y., Parsad, D., Taieb, A., Picardo, M., Ezzedine, K. and Group, V. G. I. C. (2015) 'Developing core outcome set for vitiligo clinical trials: international e-Delphi consensus', *Pigment Cell Melanoma Res*, 28(3), pp. 363-9.

- Elliott, V. J., Rodgers, D. L. and Brett, S. J. (2011) 'Systematic review of quality of life and other patient-centred outcomes after cardiac arrest survival', *Resuscitation*, 82(3), pp. 247-56.
- Fabricius, M., Pickard, R. and McColl, E. (2015) 'Is reviewing trial protocols on clinicaltrials.gov a feasible method of compiling a long-list for a core outcome set', *Trials*, 16((Suppl 3)), pp. P6.
- Felson, D. 'A CORE SET OF DISEASE-ACTIVITY MEASURES FOR RHEUMATOID-ARTHRITIS (RA) CLINICAL-TRIALS'. *Arthritis and Rheumatism*: LIPPINCOTT-RAVEN PUBL 227 EAST WASHINGTON SQ, PHILADELPHIA, PA 19106, S203-S203.
- Felson, D. T., Anderson, J. J., Boers, M., Bombardier, C., Chernoff, M., Fried, B., Furst, D., Goldsmith, C., Kieszak, S. and Lightfoot, R. (1993) 'The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. The Committee on Outcome Measures in Rheumatoid Arthritis Clinical Trials', *Arthritis Rheum*, 36(6), pp. 729-40.
- Fitch, K., Bernstein, S. J., Aguilar, M. D., Burnand, B. and LaCalle, J. R. (2001) *The RAND/UCLA appropriateness method user's manual*: DTIC Document.
- French, D., Maissi, E. and Marteau, T. M. (2005) 'The purpose of attributing cause: beliefs about the causes of myocardial infarction', *Soc Sci Med*, 60(7), pp. 1411-21.
- Friedman, L. M., Furberg, C. D. and DeMets, D. (2010) *Fundamentals of Clinical Trials*. Springer New York.
- Fries, J. F., Spitz, P., Kraines, R. G. and Holman, H. R. (1980) 'Measurement of patient outcome in arthritis', *Arthritis Rheum*, 23(2), pp. 137-45.
- Frost, N. (2011) *Qualitative research methods in psychology: Combining core approaches*. McGraw-Hill Education (UK).
- Furlong, W. J., Feeny, D. H., Torrance, G. W. and Barr, R. D. (2001) 'The Health Utilities Index (HUI) system for assessing health-related quality of life in clinical studies', *Ann Med*, 33(5), pp. 375-84.
- Gargon, E., Altman, D. G., Blazeby, J. M., Clarke, M. and Williamson, P. R. (2015a) 'COMET IV meeting summary', *Trials*, 16.
- Gargon, E., Gurung, B., Medley, N., Altman, D. G., Blazeby, J. M., Clarke, M. and Williamson, P. R. (2014) 'Choosing important health outcomes for comparative effectiveness research: a systematic review', *PLoS One*, 9(6), pp. e99111.
- Gargon, E., Williamson, P. R. and Clarke, M. (2015b) 'Collating the knowledge base for core outcome set development: developing and appraising the search strategy for a systematic review', *BMC Med Res Methodol*, 15(1), pp. 26.
- Garratt, A., Schmidt, L., Mackintosh, A. and Fitzpatrick, R. (2002) 'Quality of life measurement: bibliographic study of patient assessed health outcome measures', *BMJ*, 324(7351), pp. 1417.
- Gladman, D. D., Mease, P. J., Strand, V., Healy, P., Helliwell, P. S., Fitzgerald, O., Gottlieb, A. B., Krueger, G. G., Nash, P., Ritchlin, C. T., Taylor, W., Adebajo, A., Braun, J., Cauli, A., Carneiro, S., Choy, E., Dijkmans, B., Espinoza, L., van der Heijde, D., Husni, E., Lubrano, E., McGonagle, D., Qureshi, A., Soriano, E. R. and Zochling, J. (2007)

- 'Consensus on a core set of domains for psoriatic arthritis', *J Rheumatol*, 34(5), pp. 1167-70.
- Glaser, B. G. and Strauss, A. L. (2009) *The discovery of grounded theory: Strategies for qualitative research*. Transaction Publishers.
- Glasziou, P., Altman, D. G., Bossuyt, P., Boutron, I., Clarke, M., Julious, S., Michie, S., Moher, D. and Wager, E. (2014) 'Reducing waste from incomplete or unusable reports of biomedical research', *The Lancet*, 383(9913), pp. 267-276.
- Godwin, M., Ruhland, L., Casson, I., MacDonald, S., Delva, D., Birtwhistle, R., Lam, M. and Seguin, R. (2003) 'Pragmatic controlled clinical trials in primary care: the struggle between external and internal validity', *BMC Med Res Methodol*, 3, pp. 28.
- Gorst, S. L., Gargon, E., Clarke, M., Blazeby, J. M., Altman, D. G. and Williamson, P. R. (2016) 'Choosing Important Health Outcomes for Comparative Effectiveness Research: An Updated Review and User Survey', *PLoS One*, 11(1), pp. e0146444.
- Green, C. P., Porter, C. B., Bresnahan, D. R. and Spertus, J. A. (2000) 'Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure', *J Am Coll Cardiol*, 35(5), pp. 1245-55.
- Griffiths, F. (2009) *Research methods for health care practice*. Sage.
- Griffiths, F., Mason, V., Boardman, F., Dennick, K., Haywood, K., Achten, J., Parsons, N., Griffin, X. and Costa, M. (2015) 'Evaluating recovery following hip fracture: a qualitative interview study of what is important to patients', *BMJ Open*, 5(1), pp. e005406.
- Grimes, D. A. and Schulz, K. F. (2002) 'An overview of clinical research: the lay of the land', *Lancet*, 359(9300), pp. 57-61.
- Gräsner, J. T., Herlitz, J., Koster, R. W., Rosell-Ortiz, F., Stamatakis, L. and Bossaert, L. (2011) 'Quality management in resuscitation--towards a European cardiac arrest registry (EuReCa)', *Resuscitation*, 82(8), pp. 989-94.
- Guyatt, G. H., Oxman, A. D., Kunz, R., Atkins, D., Brozek, J., Vist, G., Alderson, P., Glasziou, P., Falck-Ytter, Y. and Schünemann, H. J. (2011) 'GRADE guidelines: 2. Framing the question and deciding on important outcomes', *J Clin Epidemiol*, 64(4), pp. 395-400.
- Halcomb, E., Davidson, P. and Hardaker, L. (2008) 'Using the consensus development conference method in healthcare research', *Nurse Res*, 16(1), pp. 56-71.
- Hammond, M., Howarth, J. and Keat, R. (1991) *Understanding phenomenology*. Oxford: Basil Blackwell.
- Harman, N. L., Bruce, I. A., Callery, P., Tierney, S., Sharif, M. O., O'Brien, K. and Williamson, P. R. (2013) 'MOMENT -- Management of Otitis Media with Effusion in Cleft Palate: protocol for a systematic review of the literature and identification of a core outcome set using a Delphi survey', *Trials*, 14(1), pp. 70.
- Harman, N. L., Bruce, I. A., Kirkham, J. J., Tierney, S., Callery, P., O'Brien, K., Bennett, A. M., Chorbachi, R., Hall, P. N., Harding-Bell, A., Parfekt, V. H., Rumsey, N., Sell, D., Sharma, R. and Williamson, P. R. (2015) 'The Importance of Integration of Stakeholder Views in Core Outcome

- Set Development: Otitis Media with Effusion in Children with Cleft Palate', *PLoS One*, 10(6), pp. e0129514.
- Hasson, F. and Keeney, S. (2011) 'Enhancing rigour in the Delphi technique research', *Technological Forecasting and Social Change*, 78(9), pp. 1695-1704.
- Hasson, F., Keeney, S. and McKenna, H. (2000) 'Research guidelines for the Delphi survey technique', *J Adv Nurs*, 32(4), pp. 1008-15.
- Hausman, D. M. (2015) *Valuing health: Well-being, freedom, and suffering*. Oxford University Press.
- Hawthorne, G., Mouthaan, J., Forbes, D. and Novaco, R. W. (2006) 'Response categories and anger measurement: do fewer categories result in poorer measurement?', *Social Psychiatry and Psychiatric Epidemiology*, 41(2), pp. 164-172.
- Hayes, H., Buckland, S. and Tarpey, M. 2012. Briefing notes for researchers: public involvement in NHS, public health and social care research. Eastleigh, Hampshire: INVOLVE.
- Haywood, K. (2010) 'The measurement of patient-reported outcome in the rheumatic diseases', in Dziedzic, K. & Hammond, A. (eds.) *Rheumatology Evidence-Based Practice for Physiotherapists and Occupational Therapists*. 1 ed: Churchill Livingstone, pp. 35-62.
- Haywood, K. L., Garratt, A. M., Dziedzic, K. and Dawes, P. T. (2003) 'Patient centered assessment of ankylosing spondylitis-specific health related quality of life: evaluation of the Patient Generated Index', *J Rheumatol*, 30(4), pp. 764-73.
- Haywood, K. L., Griffin, X. L., Achten, J. and Costa, M. L. (2014a) 'Developing a core outcome set for hip fracture trials', *Bone Joint J*, 96-B(8), pp. 1016-23.
- Haywood, K. L., Staniszewska, S. and Chapman, S. (2012) 'Quality and acceptability of patient-reported outcome measures used in chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME): a systematic review', *Qual Life Res*, 21(1), pp. 35-52.
- Haywood, K. L., Whitehead, L. and Perkins, G. D. (2014b) 'The psychosocial outcomes of cardiac arrest: Relevant and robust patient-centred assessment is essential', *Resuscitation*, 85(6), pp. 718-9.
- Herlitz, J., Alem, A. v., Wenzel, V. and Wegscheider, K. (2007) 'The methodology of clinical resuscitation research', in Paradis, N.A., Halperin, H.R., Kern, K.B., Wenzel, V. & Chamberlain, D.A. (eds.) *Cardiac Arrest: The Science and Practice of Resuscitation Medicine*: Cambridge University Press, pp. 206-215.
- Herrett, E., Smeeth, L., Walker, L., Weston, C. and Group, M. A. (2010) 'The Myocardial Ischaemia National Audit Project (MINAP)', *Heart*, 96(16), pp. 1264-7.
- Hewlett, S. A. (2003) 'Patients and clinicians have different perspectives on outcomes in arthritis', *J Rheumatol*, 30(4), pp. 877-9.
- Higgins, J. P. and Green, S. (2008) 'Defining the review question and developing criteria for including studies', *Cochrane Handbook for Systematic Reviews of Interventions*. Version, 5(0).

- Holloway, I. and Wheeler, S. (2013) *Qualitative research in nursing and healthcare*. John Wiley & Sons.
- Howells, N. R., Murray, J. R., Wylde, V., Blom, A. W. and Dieppe, P. (2014) 'Ongoing pain after knee replacement: a case controlled analysis', *Osteoarthritis and Cartilage*, 22, Supplement, pp. S410-S411.
- Hsu, C.-C. and Sandford, B. A. (2007a) 'Minimizing non-response in the Delphi process: How to respond to non-response', *Practical Assessment, Research & Evaluation*, 12(17), pp. 62-78.
- Hsu, C.-C. and Sandford, B. A. (2007b) 'The Delphi technique: making sense of consensus', *Practical Assessment, Research & Evaluation*, 12(10), pp. 1-8.
- http://www.comet-initiative.org/assets/downloads/Guidance_for_trialists.pdf cited (cited 11.06.16).
- <http://www.comet-initiative.org/resources/PlainLanguageSummary> (cited on 14.07.16).
- <http://www.ichom.org/who-we-are/> (cited on 16.05.16).
- (
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/513157/NHSOF_at_a_glance.pdf (cited on 20.06.16)
 (Accessed: cited on 20.06.16.
- Huber, M., Kottnerus, J. A., Green, L., van der Horst, H., Jadad, A. R., Kromhout, D., Leonard, B., Lorig, K., Loureiro, M. I., van der Meer, J. W., Schnabel, P., Smith, R., van Weel, C. and Smid, H. (2011) 'How should we define health?', *BMJ*, 343, pp. d4163.
- Hutchings, A., Raine, R., Sanderson, C. and Black, N. (2006) 'A comparison of formal consensus methods used for developing clinical guidelines', *J Health Serv Res Policy*, 11(4), pp. 218-24.
- Hutton, J. and Williamson, P. R. (2000) 'Bias in meta-analysis due to outcome variable selection within studies', *Journal of the Royal Statistical Society: Series C (Applied Statistics)*, 49(3), pp. 359-370.
- Idzerda, L., Rader, T., Tugwell, P. and Boers, M. (2014) 'Can we decide which outcomes should be measured in every clinical trial? A scoping review of the existing conceptual frameworks and processes to develop core outcome sets', *J Rheumatol*, 41(5), pp. 986-93.
- Jacobs, I., Nadkarni, V., Bahr, J., Berg, R. A., Billi, J. E., Bossaert, L., Cassan, P., Coovadia, A., D'Este, K., Finn, J., Halperin, H., Handley, A., Herlitz, J., Hickey, R., Idris, A., Kloeck, W., Larkin, G. L., Mancini, M. E., Mason, P., Mears, G., Monsieurs, K., Montgomery, W., Morley, P., Nichol, G., Nolan, J., Okada, K., Perlman, J., Shuster, M., Steen, P. A., Sterz, F., Tibballs, J., Timerman, S., Truitt, T., Zideman, D. and Resuscitation, I. L. C. o. (2004) 'Cardiac arrest and cardiopulmonary resuscitation outcome reports: update and simplification of the Utstein templates for resuscitation registries. A statement for healthcare professionals from a task force of the international liaison committee on resuscitation (American Heart Association, European Resuscitation Council, Australian Resuscitation Council, New Zealand Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa)', *Resuscitation*, 63(3), pp. 233-49.

- Jennett, B., Snoek, J., Bond, M. R. and Brooks, N. (1981) 'Disability after severe head injury: observations on the use of the Glasgow Outcome Scale', *J Neurol Neurosurg Psychiatry*, 44(4), pp. 285-93.
- Jette, A. M. (2006) 'Toward a common language for function, disability, and health', *Phys Ther*, 86(5), pp. 726-34.
- Jones, J. and Hunter, D. (1995) 'Consensus methods for medical and health services research', *BMJ*, 311(7001), pp. 376-80.
- Jørgensen, M. W. and Phillips, L. J. (2002) *Discourse analysis as theory and method*. Sage.
- Kamper, S. J., Stanton, T. R., Williams, C. M., Maher, C. G. and Hush, J. M. (2011) 'How is recovery from low back pain measured? A systematic review of the literature', *Eur Spine J*, 20(1), pp. 9-18.
- Karas, J., Ashkenazi, S., Guarino, A., Lo Vecchio, A., Shamir, R., Vandenplas, Y., Szajewska, H. and (COMMENT), o. b. o. t. C. G. o. O. M. M. i. P. E. N. C. T. (2014) 'A core outcome set for clinical trials in acute diarrhoea', *Arch Dis Child*.
- Keeley, T., Khan, H., Pinfold, V., Williamson, P., Mathers, J., Davies, L., Sayers, R., England, E., Reilly, S., Byng, R., Gask, L., Clark, M., Huxley, P., Lewis, P., Birchwood, M. and Calvert, M. (2015) 'Core outcome sets for use in effectiveness trials involving people with bipolar and schizophrenia in a community-based setting (PARTNERS2): study protocol for the development of two core outcome sets', *Trials*, 16(1), pp. 47.
- Keeley, T., Williamson, P., Callery, P., Jones, L. L., Mathers, J., Jones, J., Young, B. and Calvert, M. (2016) 'The use of qualitative methods to inform Delphi surveys in core outcome set development', *Trials*, 17(1), pp. 230.
- Keener, A. B. (2014) 'Group seeks standardization for what clinical trials must measure', *Nat Med*, 20(8), pp. 798-9.
- Kelley, T. A. (2015) 'International Consortium for Health Outcomes Measurement (ICHOM)', *Trials*, 16(Suppl 3), pp. O4.
- Ketilsdottir, A., Albertsdottir, H. R., Akadottir, S. H., Gunnarsdottir, T. J. and Jonsdottir, H. (2014) 'The experience of sudden cardiac arrest: becoming reawakened to life', *Eur J Cardiovasc Nurs*, 13(5), pp. 429-35.
- Khanna, D., Lovell, D. J., Giannini, E., Clements, P. J., Merkel, P. A., Seibold, J. R., Matucci-Cerinic, M., Denton, C. P., Mayes, M. D., Steen, V. D., Varga, J., Furst, D. E. and co-authors, S. C. T. C. (2008) 'Development of a provisional core set of response measures for clinical trials of systemic sclerosis', *Ann Rheum Dis*, 67(5), pp. 703-9.
- Kirkham, J. J., Boers, M., Tugwell, P., Clarke, M. and Williamson, P. R. (2013a) 'Outcome measures in rheumatoid arthritis randomised trials over the last 50 years', *Trials*, 14(1), pp. 324.
- Kirkham, J. J., Dwan, K. M., Altman, D. G., Gamble, C., Dodd, S., Smyth, R. and Williamson, P. R. (2010) 'The impact of outcome reporting bias in randomised controlled trials on a cohort of systematic reviews', *BMJ*, 340, pp. c365.
- Kirkham, J. J., Gargon, E., Clarke, M. and Williamson, P. R. (2013b) 'Can a core outcome set improve the quality of systematic reviews? - a

- survey of the Co-ordinating Editors of Cochrane review groups', *Trials*, 14, pp. 21.
- Kirkham, J. J., Gorst, S., Altman, D. G., Blazeby, J., Clarke, M., Devane, D., Gargon, E., Williamson, P. R. and Group, C.-S. (2015) 'COS-STAR: a reporting guideline for studies developing core outcome sets (protocol)', *Trials*, 16, pp. 373.
- Kirwan, J., Heiberg, T., Hewlett, S., Hughes, R., Kvien, T., Ahlmén, M., Boers, M., Minnock, P., Saag, K. and Shea, B. (2003) 'Outcomes from the patient perspective workshop at OMERACT 6', *The Journal of rheumatology*, 30(4), pp. 868-872.
- Kirwan, J. R., Minnock, P., Adebajo, A., Bresnihan, B., Choy, E., de Wit, M., Hazes, M., Richards, P., Saag, K., Suarez-Almazor, M., Wells, G. and Hewlett, S. (2007) 'Patient perspective: fatigue as a recommended patient centered outcome measure in rheumatoid arthritis', *J Rheumatol*, 34(5), pp. 1174-7.
- Kleinman, M. E., Chameides, L., Schexnayder, S. M., Samson, R. A., Hazinski, M. F., Atkins, D. L., Berg, M. D., de Caen, A. R., Fink, E. L., Freid, E. B., Hickey, R. W., Marino, B. S., Nadkarni, V. M., Proctor, L. T., Qureshi, F. A., Sartorelli, K., Topjian, A., van der Jagt, E. W. and Zaritsky, A. L. (2010) 'Part 14: pediatric advanced life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care', *Circulation*, 122(18 Suppl 3), pp. S876-908.
- Koroshetz, W. (2015) 'A core set of trial outcomes for every medical discipline?', *BMJ*, 350, pp. h85.
- Kostanjsek, N. (2011) 'Use of The International Classification of Functioning, Disability and Health (ICF) as a conceptual framework and common language for disability statistics and health information systems', *BMC Public Health*, 11 Suppl 4, pp. S3.
- Kragholm, K., Skovmoeller, M., Christensen, A. L., Fonager, K., Tilsted, H. H., Kirkegaard, H., DE Haas, I. and Rasmussen, B. S. (2013) 'Employment status 1 year after out-of-hospital cardiac arrest in comatose patients treated with therapeutic hypothermia', *Acta Anaesthesiol Scand*, 57(7), pp. 936-43.
- Krousel-Wood, M. A. (1999) 'Practical considerations in the measurement of outcomes in healthcare', *Ochsner J*, 1(4), pp. 187-94.
- Krüger, A. J., Lockey, D., Kurola, J., Di Bartolomeo, S., Castrén, M., Mikkelsen, S. and Lossius, H. M. (2011) 'A consensus-based template for documenting and reporting in physician-staffed pre-hospital services', *Scand J Trauma Resusc Emerg Med*, 19, pp. 71.
- Langendam, M. W., Akl, E. A., Dahm, P., Glasziou, P., Guyatt, G. and Schünemann, H. J. (2013) 'Assessing and presenting summaries of evidence in Cochrane Reviews', *Syst Rev*, 2, pp. 81.
- Larkin, M., Watts, S. and Clifton, E. (2006) 'Giving voice and making sense in interpretative phenomenological analysis', *Qualitative Research in Psychology*, 3(2), pp. 102-120.
- Laughlin, G. 1969. SMOG Grading- a new readability formula. *Journal of Reading*.
- Lilja, G., Nilsson, G., Nielsen, N., Friberg, H., Hassager, C., Koopmans, M., Kuiper, M., Martini, A., Mellinghoff, J., Pelosi, P., Wanscher, M., Wise,

- M. P., Östman, I. and Cronberg, T. (2015) 'Anxiety and depression among out-of-hospital cardiac arrest survivors', *Resuscitation*, 97, pp. 68-75.
- Lundgren-Nilsson, A., Rosén, H., Hofgren, C. and Sunnerhagen, K. S. (2005) 'The first year after successful cardiac resuscitation: function, activity, participation and quality of life', *Resuscitation*, 66(3), pp. 285-9.
- Macefield, R. C., Avery, K. N. and Blazeby, J. M. (2013) 'Integration of clinical and patient-reported outcomes in surgical oncology', *Br J Surg*, 100(1), pp. 28-37.
- MacKichan, F., Wylde, V. and Gooberman-Hill, R. (2014) 'Service provision for patients with chronic post-surgical pain after total knee replacement: a qualitative study of healthcare provider perspectives', *Osteoarthritis and Cartilage*, 22, Supplement, pp. S225-S226.
- MacLennan, S., Bekema, H. J., Williamson, P. R., Campbell, M. K., Stewart, F., MacLennan, S. J., N'Dow, J. M. and Lam, T. B. (2015) 'A core outcome set for localised prostate cancer effectiveness trials: protocol for a systematic review of the literature and stakeholder involvement through interviews and a Delphi survey', *Trials*, 16(1), pp. 76.
- Macleod, M. R., Michie, S., Roberts, I., Dirnagl, U., Chalmers, I., Ioannidis, J. P., Al-Shahi Salman, R., Chan, A. W. and Glasziou, P. (2014) 'Biomedical research: increasing value, reducing waste', *Lancet*, 383(9912), pp. 101-4.
- Magnusson, E. and Marecek, J. (2015) *Doing Interview-based Qualitative Research: A Learner's Guide*. Cambridge University Press.
- MAHONEY, F. I. and BARTHEL, D. W. (1965) 'FUNCTIONAL EVALUATION: THE BARTHEL INDEX', *Md State Med J*, 14, pp. 61-5.
- Marshall, S., Haywood, K. and Fitzpatrick, R. (2006) 'Impact of patient-reported outcome measures on routine practice: a structured review', *J Eval Clin Pract*, 12(5), pp. 559-68.
- McCann, L. J., Kirkham, J. J., Wedderburn, L. R., Pilkington, C., Huber, A. M., Ravelli, A., Appelbe, D., Williamson, P. R. and Beresford, M. W. (2015) 'Development of an internationally agreed minimal dataset for juvenile dermatomyositis (JDM) for clinical and research use', *Trials*, 16, pp. 268.
- McColl, E., Jacoby, A., Thomas, L., Soutter, J., Bamford, C., Steen, N., Thomas, R., Harvey, E., Garratt, A. and Bond, J. (2001) *Design and use of questionnaires: a review of best practice applicable to surveys of health service staff and patients*. Core Research.
- McConnell-Henry, T., Chapman, Y. and Francis, K. (2011) 'Member checking and Heideggerian phenomenology: a redundant component', *Nurse Res*, 18(2), pp. 28-37.
- McDowell, I. (2006) *Measuring Health: A Guide to rating scales and questionnaires*. Third Edition edn.: Oxford University Press.
- McFarland, L., Barlow, J. and Turner, A. (2009) 'Understanding metaphor to facilitate emotional expression during a chronic disease self-management course', *Patient Educ Couns*, 77(2), pp. 255-9.
- McGrath, P. J., Walco, G. A., Turk, D. C., Dworkin, R. H., Brown, M. T., Davidson, K., Eccleston, C., Finley, G. A., Goldschneider, K., Haverkos, L., Hertz, S. H., Ljungman, G., Palermo, T., Rappaport, B. A., Rhodes, T., Schechter, N., Scott, J., Sethna, N., Svensson, O. K.,

- Stinson, J., von Baeyer, C. L., Walker, L., Weisman, S., White, R. E., Zajicek, A., Zeltzer, L. and PedIMMPACT (2008) 'Core outcome domains and measures for pediatric acute and chronic/recurrent pain clinical trials: PedIMMPACT recommendations', *J Pain*, 9(9), pp. 771-83.
- McNamara, R. L., Spatz, E. S., Kelley, T. A., Stowell, C. J., Beltrame, J., Heidenreich, P., Tresserras, R., Jernberg, T., Chua, T., Morgan, L., Panigrahi, B., Rosas Ruiz, A., Rumsfeld, J. S., Sadwin, L., Schoeberl, M., Shahian, D., Weston, C., Yeh, R. and Lewin, J. (2015) 'Standardized Outcome Measurement for Patients With Coronary Artery Disease: Consensus From the International Consortium for Health Outcomes Measurement (ICHOM)', *J Am Heart Assoc*, 4(5).
- Mease, P., Arnold, L. M., Choy, E. H., Clauw, D. J., Crofford, L. J., Glass, J. M., Martin, S. A., Morea, J., Simon, L., Strand, C. V., Williams, D. A. and Group, O. F. W. (2009) 'Fibromyalgia syndrome module at OMERACT 9: domain construct', *J Rheumatol*, 36(10), pp. 2318-29.
- Mease, P. J., Arnold, L. M., Crofford, L. J., Williams, D. A., Russell, I. J., Humphrey, L., Abetz, L. and Martin, S. A. (2008) 'Identifying the clinical domains of fibromyalgia: contributions from clinician and patient Delphi exercises', *Arthritis Rheum*, 59(7), pp. 952-60.
- Miller, A. B., Hoogstraten, B., Staquet, M. and Winkler, A. (1981) 'Reporting results of cancer treatment', *Cancer*, 47(1), pp. 207-14.
- Moher, D., Hopewell, S., Schulz, K. F., Montori, V., Gøtzsche, P. C., Devereaux, P. J., Elbourne, D., Egger, M., Altman, D. G. and CONSORT (2012) 'CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials', *Int J Surg*, 10(1), pp. 28-55.
- Mokkink, L. B., Terwee, C. B., Patrick, D. L., Alonso, J., Stratford, P. W., Knol, D. L., Bouter, L. M. and de Vet, H. C. (2010) 'The COSMIN checklist for assessing the methodological quality of studies on measurement properties of health status measurement instruments: an international Delphi study', *Qual Life Res*, 19(4), pp. 539-49.
- Morgans, A. K., van Bommel, A. C., Stowell, C., Abrahm, J. L., Basch, E., Bekelman, J. E., Berry, D. L., Bossi, A., Davis, I. D., de Reijke, T. M., Denis, L. J., Evans, S. M., Fleshner, N. E., George, D. J., Kiefert, J., Lin, D. W., Matthew, A. G., McDermott, R., Payne, H., Roos, I. A., Schrag, D., Steuber, T., Tombal, B., van Basten, J. P., van der Hoeven, J. J., Penson, D. F. and Measurement, A. P. C. W. G. o. t. I. C. f. H. O. (2015) 'Development of a Standardized Set of Patient-centered Outcomes for Advanced Prostate Cancer: An International Effort for a Unified Approach', *Eur Urol*, 68(5), pp. 891-8.
- Morris, C., Janssens, A., Tomlinson, R., Williams, J. and Logan, S. (2013) 'Towards a definition of neurodisability: a Delphi survey', *Dev Med Child Neurol*, 55(12), pp. 1103-8.
- Moulaert, V. R., van Heugten, C. M., Winkens, B., Bakx, W. G., de Krom, M. C., Gorgels, T. P., Wade, D. T. and Verbunt, J. A. (2015) 'Early neurologically-focused follow-up after cardiac arrest improves quality of life at one year: A randomised controlled trial', *Int J Cardiol*, 193, pp. 8-16.

- Moulaert, V. R., Verbunt, J. A., van Heugten, C. M. and Wade, D. T. (2009) 'Cognitive impairments in survivors of out-of-hospital cardiac arrest: a systematic review', *Resuscitation*, 80(3), pp. 297-305.
- Moza, A., Benstoem, C., Autschbach, R., Stoppe, C. and Goetzenich, A. (2015) 'A core outcome set for all types of cardiac surgery effectiveness trials: a study protocol for an international eDelphi survey to achieve consensus on what to measure and the subsequent selection of measurement instruments', *Trials*, 16, pp. 545.
- Mozaffarian, D., Benjamin, E. J., Go, A. S., Arnett, D. K., Blaha, M. J., Cushman, M., de Ferranti, S., Després, J. P., Fullerton, H. J., Howard, V. J., Huffman, M. D., Judd, S. E., Kissela, B. M., Lackland, D. T., Lichtman, J. H., Lisabeth, L. D., Liu, S., Mackey, R. H., Matchar, D. B., McGuire, D. K., Mohler, E. R., Moy, C. S., Muntner, P., Mussolino, M. E., Nasir, K., Neumar, R. W., Nichol, G., Palaniappan, L., Pandey, D. K., Reeves, M. J., Rodriguez, C. J., Sorlie, P. D., Stein, J., Towfighi, A., Turan, T. N., Virani, S. S., Willey, J. Z., Woo, D., Yeh, R. W., Turner, M. B. and Subcommittee, A. H. A. S. C. a. S. S. (2015) 'Heart disease and stroke statistics--2015 update: a report from the American Heart Association', *Circulation*, 131(4), pp. e29-322.
- Murphy, M. K., Black, N. A., Lamping, D. L., McKee, C. M., Sanderson, C. F., Askham, J. and Marteau, T. (1998) 'Consensus development methods, and their use in clinical guideline development', *Health Technol Assess*, 2(3), pp. i-iv, 1-88.
- Negovsky, V. A. (1972) 'The second step in resuscitation—the treatment of the 'post-resuscitation' disease', *Resuscitation*, 1(1), pp. 1-7.
- Negovsky, V. A. and Gurvitch, A. M. (1995) 'Post-resuscitation disease--a new nosological entity. Its reality and significance', *Resuscitation*, 30(1), pp. 23-7.
- Newman, S. P. (1997) 'Psychosocial measures in musculoskeletal trials', *Journal of rheumatology*, 24(5), pp. 979-984.
- Nichol, G., Guffey, D., Stiell, I. G., Leroux, B., Cheskes, S., Idris, A., Kudenchuk, P. J., Macphee, R. S., Wittwer, L., Rittenberger, J. C., Rea, T. D., Sheehan, K., Rac, V. E., Raina, K., Gorman, K., Aufderheide, T. and Investigators, R. O. C. (2015) 'Post-discharge outcomes after resuscitation from out-of-hospital cardiac arrest: A ROC PRIMED substudy', *Resuscitation*, 93, pp. 74-81.
- Nichol, G., Thomas, E., Callaway, C. W., Hedges, J., Powell, J. L., Aufderheide, T. P., Rea, T., Lowe, R., Brown, T., Dreyer, J., Davis, D., Idris, A., Stiell, I. and Investigators, R. O. C. (2008) 'Regional variation in out-of-hospital cardiac arrest incidence and outcome', *JAMA*, 300(12), pp. 1423-31.
- Nielsen, N., Wetterslev, J., Cronberg, T., Erlinge, D., Gasche, Y., Hassager, C., Horn, J., Hovdenes, J., Kjaergaard, J., Kuiper, M., Pellis, T., Stammet, P., Wanscher, M., Wise, M. P., Åneman, A., Al-Subaie, N., Boesgaard, S., Bro-Jeppesen, J., Brunetti, I. and Bugge, J. F. (2013) 'Targeted temperature management at 33°C versus 36°C after cardiac arrest', *New England Journal of Medicine*, 369(23), pp. 2197-2206 10p.
- Nishiyama, C., Iwami, T., Kawamura, T., Ando, M., Yonemoto, N., Hiraide, A. and Nonogi, H. (2008) 'Effectiveness of simplified chest compression-

- only CPR training for the general public: a randomized controlled trial', *Resuscitation*, 79(1), pp. 90-6.
- Noc, M., Bendz, B. and Kern, K. B. (2007) 'Percutaneous coronary intervention (PCI) after successful reestablishment of spontaneous circulation and during cardiopulmonary resuscitation', in Paradis, N.A., Halperin, H.R., Kern, K.B., Wenzel, V. & Chamberlain, D.A. (eds.) *Cardiac Arrest: The Science and Practice of Resuscitation Medicine*: Cambridge University Press, pp. 764-771.
- Nolan, J., Soar, J. and Eikeland, H. (2006) 'The chain of survival', *Resuscitation*, 71(3), pp. 270-1.
- Nolan, J. P., Hazinski, M. F., Aickin, R., Bhanji, F., Billi, J. E., Callaway, C. W., Castren, M., de Caen, A. R., Ferrer, J. M., Finn, J. C., Gent, L. M., Griffin, R. E., Iverson, S., Lang, E., Lim, S. H., Maconochie, I. K., Montgomery, W. H., Morley, P. T., Nadkarni, V. M., Neumar, R. W., Nikolaou, N. I., Perkins, G. D., Perlman, J. M., Singletary, E. M., Soar, J., Travers, A. H., Welsford, M., Wyllie, J. and Zidean, D. A. (2015) 'Part 1: Executive summary: 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations', *Resuscitation*, 95, pp. e1-31.
- Nolan, J. P., Soar, J., Smith, G. B., Gwinnutt, C., Parrott, F., Power, S., Harrison, D. A., Nixon, E., Rowan, K. and Audit, N. C. A. (2014) 'Incidence and outcome of in-hospital cardiac arrest in the United Kingdom National Cardiac Arrest Audit', *Resuscitation*, 85(8), pp. 987-92.
- O'Boyle, C., McGee, H., Hickey, A., Joyce, C., Browne, J., O'Malley, K. and Hiltbrunner, B. (1993) 'The Schedule for the Evaluation of Individual Quality of Life (SEIQoL). Administration Manual'.
- Organization, W. H. (1980) 'International classification of impairments, disabilities, and handicaps: a manual of classification relating to the consequences of disease, published in accordance with resolution WHA29. 35 of the Twenty-ninth World Health Assembly, May 1976'.
- Ornato, J. P., Becker, L. B., Weisfeldt, M. L. and Wright, B. A. (2010) 'Cardiac arrest and resuscitation: an opportunity to align research prioritization and public health need', *Circulation*, 122(18), pp. 1876-9.
- Osborn, M. and Smith, J. A. (1998) 'The personal experience of chronic benign lower back pain: An interpretative phenomenological analysis', *British Journal of Health Psychology*, 3(1), pp. 65-83.
- Palacios-Cena, D., Losa-Iglesias, M. E., Salvadores-Fuentes, P. and Fernandez-de-las-Penas, C. (2011) 'Sudden cardiac death: the perspectives of Spanish survivors', *Nursing & Health Sciences*, 13(2), pp. 149-55.
- Patrick, D. L., Burke, L. B., Powers, J. H., Scott, J. A., Rock, E. P., Dawisha, S., O'Neill, R. and Kennedy, D. L. (2007) 'Patient-reported outcomes to support medical product labeling claims: FDA perspective', *Value Health*, 10 Suppl 2, pp. S125-37.
- Perkins, G. D. and Cooke, M. W. (2012) 'Variability in cardiac arrest survival: the NHS Ambulance Service Quality Indicators', *Emerg Med J*, 29(1), pp. 3-5.

- Perkins, G. D., Jacobs, I. G., Nadkarni, V. M., Berg, R. A., Bhanji, F., Biarent, D., Bossaert, L. L., Brett, S. J., Chamberlain, D., de Caen, A. R., Deakin, C. D., Finn, J. C., Gräsner, J. T., Hazinski, M. F., Iwami, T., Koster, R. W., Lim, S. H., Ma, M. H., McNally, B. F., Morley, P. T., Morrison, L. J., Monsieurs, K. G., Montgomery, W., Nichol, G., Okada, K., Ong, M. E., Travers, A. H. and Nolan, J. P. (2014) 'Cardiac arrest and cardiopulmonary resuscitation outcome reports: Update of the Utstein resuscitation registry templates for out-of-hospital cardiac arrest', *Resuscitation*.
- Perkins, G. D., Woollard, M., Cooke, M. W., Deakin, C., Horton, J., Lall, R., Lamb, S. E., McCabe, C., Quinn, T., Slowther, A. and Gates, S. (2010) 'Prehospital randomised assessment of a mechanical compression device in cardiac arrest (PaRAMeDIC) trial protocol', *Scandinavian journal of trauma, resuscitation and emergency medicine*, 18, pp. 58 [Randomized Controlled Trial; Research Support, Non-U.S. Gov't].
- Pope, C. and Mays, N. (1995) 'Reaching the parts other methods cannot reach: an introduction to qualitative methods in health and health services research', *BMJ*, 311(6996), pp. 42-5.
- Porter, M. E. (2010) 'What is value in health care?', *N Engl J Med*, 363(26), pp. 2477-81.
- Potter, M., Gordon, S. and Hamer, P. 2004. The nominal group technique: A useful consensus methodology in physiotherapy research. *New Zealand Journal of Physiotherapy*.
- Potter, S., Brigid, A., Whiting, P. F., Cawthorn, S. J., Avery, K. N., Donovan, J. L. and Blazeby, J. M. (2011) 'Reporting clinical outcomes of breast reconstruction: a systematic review', *J Natl Cancer Inst*, 103(1), pp. 31-46.
- Potter, S., Holcombe, C., Ward, J. A., Blazeby, J. M. and Group, B. S. (2015a) 'Development of a core outcome set for research and audit studies in reconstructive breast surgery', *Br J Surg*, 102(11), pp. 1360-71.
- Potter, S., Mills, N., Cawthorn, S., Wilson, S. and Blazeby, J. (2015b) 'Exploring information provision in reconstructive breast surgery: A qualitative study', *Breast*, 24(6), pp. 732-8.
- Preedy, V. R. and Watson, R. R. (2010) *Handbook of disease burdens and quality of life measures*. Springer New York.
- Prinsen, C. A., Vohra, S., Rose, M. R., King-Jones, S., Ishaque, S., Bhaloo, Z., Adams, D. and Terwee, C. B. (2014) 'Core Outcome Measures in Effectiveness Trials (COMET) initiative: protocol for an international Delphi study to achieve consensus on how to select outcome measurement instruments for outcomes included in a 'core outcome set'', *Trials*, 15, pp. 247.
- Rabin, R. and de Charro, F. (2001) 'EQ-5D: a measure of health status from the EuroQol Group', *Ann Med*, 33(5), pp. 337-43.
- Raina, K. D., Callaway, C., Rittenberger, J. C. and Holm, M. B. (2008) 'Neurological and functional status following cardiac arrest: method and tool utility', *Resuscitation*, 79(2), pp. 249-56.

- Raina, K. D., Rittenberger, J. C., Holm, M. B. and Callaway, C. W. (2015) 'Functional Outcomes: One Year after a Cardiac Arrest', *Biomed Res Int*, 2015, pp. 283608.
- Raine, R., Sanderson, C. and Black, N. (2005) 'Developing clinical guidelines: a challenge to current methods', *BMJ*, 331(7517), pp. 631-3.
- RANKIN, J. (1957) 'Cerebral vascular accidents in patients over the age of 60. I. General considerations', *Scott Med J*, 2(4), pp. 127-36.
- Reay, H., Arulkumaran, N. and Brett, S. J. (2014) 'Priorities for Future Intensive Care Research in the UK: Results of a James Lind Alliance Priority Setting Partnership', *Journal of the Intensive Care Society*, 15(4), pp. 288-296.
- Rector, T. and Cohn, J. 2004. Minnesota living with heart failure questionnaire.
- Rector, T. S., Kubo, S. H. and Cohn, J. N. (1987) 'Patients' self-assessment of their congestive heart failure. Part 2: Content, reliability and validity of a new measure, the Minnesota Living with Heart Failure questionnaire.', *Heart Failure*, (Oct/Nov), pp. 198-209.
- Reeves, S., Kuper, A. and Hodges, B. D. (2008) 'Qualitative research methodologies: ethnography', *BMJ*, 337, pp. a1020.
- Richardson, F. M. (1972) 'Peer review of medical care', *Med Care*, 10(1), pp. 29-39.
- Ringdal, K. G., Coats, T. J., Lefering, R., Di Bartolomeo, S., Steen, P. A., Røise, O., Handolin, L., Lossius, H. M. and panel, U. T. e. (2008) 'The Utstein template for uniform reporting of data following major trauma: a joint revision by SCANTEM, TARN, DGU-TR and RITG', *Scand J Trauma Resusc Emerg Med*, 16, pp. 7.
- Ritchie, J., Lewis, J., Nicholls, C. M. and Ormston, R. (2013) *Qualitative research practice: A guide for social science students and researchers*. Sage.
- Ritchie, J. and Spencer, L. (2002) 'Qualitative data analysis for applied policy research', *The qualitative researcher's companion*, pp. 305-329.
- Ruperto, N., Ravelli, A., Murray, K. J., Lovell, D. J., Andersson-Gare, B., Feldman, B. M., Garay, S., Kuis, W., Machado, C., Pachman, L., Prieur, A. M., Rider, L. G., Silverman, E., Tsitsami, E., Woo, P., Giannini, E. H., Martini, A., (PRINTO), P. R. I. T. O. and (PRCSG), P. R. C. S. G. (2003) 'Preliminary core sets of measures for disease activity and damage assessment in juvenile systemic lupus erythematosus and juvenile dermatomyositis', *Rheumatology (Oxford)*, 42(12), pp. 1452-9.
- Ruta, D. A., Garratt, A. M., Leng, M., Russell, I. T. and MacDonald, L. M. (1994) 'A new approach to the measurement of quality of life. The Patient-Generated Index', *Med Care*, 32(11), pp. 1109-26.
- Sackett, D. L. (1997) 'Evidence-based medicine', *Semin Perinatol*, 21(1), pp. 3-5.
- Saketkoo, L. A., Mittoo, S., Frankel, S., LeSage, D., Sarver, C., Phillips, K., Strand, V., Matteson, E. L., Group, O. C. T. D. I. L. D. W. and Group, O. C. T. D.-I. L. D. W. (2014a) 'Reconciling healthcare professional and patient perspectives in the development of disease activity and

- response criteria in connective tissue disease-related interstitial lung diseases', *J Rheumatol*, 41(4), pp. 792-8.
- Saketkoo, L. A., Mittoo, S., Huscher, D., Khanna, D., Dellaripa, P. F., Distler, O., Flaherty, K. R., Frankel, S., Oddis, C. V., Denton, C. P., Fischer, A., Kowal-Bielecka, O. M., LeSage, D., Merkel, P. A., Phillips, K., Pittrow, D., Swigris, J., Antoniou, K., Baughman, R. P., Castellino, F. V., Christmann, R. B., Christopher-Stine, L., Collard, H. R., Cottin, V., Danoff, S., Highland, K. B., Hummers, L., Shah, A. A., Kim, D. S., Lynch, D. A., Miller, F. W., Proudman, S. M., Richeldi, L., Ryu, J. H., Sandorfi, N., Sarver, C., Wells, A. U., Strand, V., Matteson, E. L., Brown, K. K., Seibold, J. R. and Group, C.-I. S. I. (2014b) 'Connective tissue disease related interstitial lung diseases and idiopathic pulmonary fibrosis: provisional core sets of domains and instruments for use in clinical trials', *Thorax*, 69(5), pp. 428-36.
- Salinas, J., Sprinkhuizen, S. M., Ackerson, T., Bernhardt, J., Davie, C., George, M. G., Gething, S., Kelly, A. G., Lindsay, P., Liu, L., Martins, S. C., Morgan, L., Norrving, B., Ribbers, G. M., Silver, F. L., Smith, E. E., Williams, L. S. and Schwamm, L. H. (2016) 'An International Standard Set of Patient-Centered Outcome Measures After Stroke', *Stroke*, 47(1), pp. 180-6.
- Sanderson, T., Morris, M., Calnan, M., Richards, P. and Hewlett, S. (2010a) 'Patient perspective of measuring treatment efficacy: the rheumatoid arthritis patient priorities for pharmacologic interventions outcomes', *Arthritis Care Res (Hoboken)*, 62(5), pp. 647-56.
- Sanderson, T., Morris, M., Calnan, M., Richards, P. and Hewlett, S. (2010b) 'What outcomes from pharmacologic treatments are important to people with rheumatoid arthritis? Creating the basis of a patient core set', *Arthritis Care Res (Hoboken)*, 62(5), pp. 640-6.
- Sandroni, C., Nolan, J., Cavallaro, F. and Antonelli, M. (2007) 'In-hospital cardiac arrest: incidence, prognosis and possible measures to improve survival', *Intensive Care Med*, 33(2), pp. 237-45.
- Sauvé, M. J., Doolittle, N., Walker, J. A., Paul, S. M. and Scheinman, M. M. (1996a) 'Factors associated with cognitive recovery after cardiopulmonary resuscitation', *Am J Crit Care*, 5(2), pp. 127-39.
- Sauvé, M. J., Walker, J. A., Massa, S. M., Winkle, R. A. and Scheinman, M. M. (1996b) 'Patterns of cognitive recovery in sudden cardiac arrest survivors: the pilot study', *Heart Lung*, 25(3), pp. 172-81.
- Sawyer, K. N. and Kurz, M. C. (2015) 'Assessing cardiac arrest beyond hospital discharge--We are only as "Good" as the outcomes we measure', *Resuscitation*, 94, pp. A1-2.
- Scarborough, P., Bhatnagar, P., Wickramasinghe, K., Smolina, K., Mitchell, C. and Rayner, M. (2010) *Coronary Heart Disease Statistics 2010*. Department of Public Health, University of Oxford: British Heart Foundation Health Promotion Research Group.
- Schmitt, J., Apfelbacher, C., Spuls, P. I., Thomas, K. S., Simpson, E. L., Furue, M., Chalmers, J. and Williams, H. C. (2015) 'The Harmonizing Outcome Measures for Eczema (HOME) roadmap: a methodological framework to develop core sets of outcome measurements in dermatology', *J Invest Dermatol*, 135(1), pp. 24-30.

- Schmitt, J., Langan, S., Stamm, T., Williams, H. C. and panel, H. O. M. i. E. H. D. (2011) 'Core outcome domains for controlled trials and clinical recordkeeping in eczema: international multiperspective Delphi consensus process', *J Invest Dermatol*, 131(3), pp. 623-30.
- Schmitt, J., Spuls, P., Boers, M., Thomas, K., Chalmers, J., Roekevisch, E., Schram, M., Allsopp, R., Aoki, V., Apfelbacher, C., Bruijnzeel-Koomen, C., Bruin-Weller, M., Charman, C., Cohen, A., Dohil, M., Flohr, C., Furue, M., Gieler, U., Hooft, L., Humphreys, R., Ishii, H. A., Katayama, I., Kouwenhoven, W., Langan, S., Lewis-Jones, S., Merhand, S., Murota, H., Murrell, D. F., Nankervis, H., Ohya, Y., Oranje, A., Otsuka, H., Paul, C., Rosenbluth, Y., Saeki, H., Schuttelaar, M. L., Stalder, J. F., Svensson, A., Takaoka, R., Wahlgren, C. F., Weidinger, S., Wollenberg, A. and Williams, H. (2012) 'Towards global consensus on outcome measures for atopic eczema research: results of the HOME II meeting', *Allergy*, 67(9), pp. 1111-7.
- Schmitt, J., Williams, H. and Group, H. D. (2010) 'Harmonising Outcome Measures for Eczema (HOME). Report from the First International Consensus Meeting (HOME 1), 24 July 2010, Munich, Germany', *Br J Dermatol*, 163(6), pp. 1166-8.
- Schulz, K. F., Altman, D. G., Moher, D. and Group, C. (2011) 'CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials', *Int J Surg*, 9(8), pp. 672-7.
- Schumacher, H. R., Taylor, W., Edwards, L., Grainger, R., Schlesinger, N., Dalbeth, N., Sivera, F., Singh, J., Evans, R., Waltrip, R. W., Diaz-Torne, C., MacDonald, P., McQueen, F. and Perez-Ruiz, F. (2009) 'Outcome domains for studies of acute and chronic gout', *J Rheumatol*, 36(10), pp. 2342-5.
- Schünemann, H., Brozek, J. and Oxman, A. (2009) 'GRADE handbook for grading quality of evidence and strength of recommendation', *The GRADE Working Group*.
- Scott, D., Panayi, G., Van Riel, P., Smolen, J. and Van de Putte, L. (1991) 'Disease activity in rheumatoid arthritis: preliminary report of the Consensus Study Group of the European Workshop for Rheumatology Research', *Clinical and experimental rheumatology*, 10(5), pp. 521-525.
- Scott, D., Spector, T., Pullar, T. and McConkey, B. (1989) 'What should we hope to achieve when treating rheumatoid arthritis?', *Annals of the rheumatic diseases*, 48(3), pp. 256.
- Scott, D. L., Panayi, G. S., van Riel, P. L., Smolen, J. and van de Putte, L. B. (1992) 'Disease activity in rheumatoid arthritis: preliminary report of the Consensus Study Group of the European Workshop for Rheumatology Research', *Clin Exp Rheumatol*, 10(5), pp. 521-5.
- Sinha, I. P., Gallagher, R., Williamson, P. R. and Smyth, R. L. (2012) 'Development of a core outcome set for clinical trials in childhood asthma: a survey of clinicians, parents, and young people', *Trials*, 13, pp. 103.
- Sinha, I. P., Smyth, R. L. and Williamson, P. R. (2011) 'Using the Delphi technique to determine which outcomes to measure in clinical trials:

- recommendations for the future based on a systematic review of existing studies', *PLoS Med*, 8(1), pp. e1000393.
- Sinha, I. P., Williamson, P. R. and Smyth, R. L. (2009) 'Outcomes in clinical trials of inhaled corticosteroids for children with asthma are narrowly focussed on short term disease activity', *PLoS One*, 4(7), pp. e6276.
- Skilton, E., Aslam, M., Yeung, J., Gao, F. and Melody, T. (2016) 'Embedding patient and public involvement within research—How to set up a research patient ambassador group within a NHS trust', *Journal of the Intensive Care Society*, pp. 1751143716644459.
- Sleat, G. K., Ardolino, A. M. and Willett, K. M. (2011) 'Outcome measures in major trauma care: a review of current international trauma registry practice', *Emerg Med J*, 28(12), pp. 1008-12.
- Smaïl-Faugeron, V., Fron Chabouis, H., Durieux, P., Attal, J. P., Muller-Bolla, M. and Courson, F. (2013) 'Development of a core set of outcomes for randomized controlled trials with multiple outcomes--example of pulp treatments of primary teeth for extensive decay in children', *PLoS One*, 8(1), pp. e51908.
- Smith, A., Joseph, S. and Das Nair, R. (2011) 'An interpretative phenomenological analysis of posttraumatic growth in adults bereaved by suicide', *Journal of Loss and Trauma*, 16(5), pp. 413-430.
- Smith, J. A. (2011) 'Evaluating the contribution of interpretative phenomenological analysis', *Health psychology review*, 5(1), pp. 9-27.
- Smith, J. A. (2015) *Qualitative psychology: A practical guide to research methods*. Sage.
- Smith, J. A., Larkin, M. H. and Flowers, P. (2009) *Interpretative phenomenological analysis : theory, method and research*. Los Angeles ; London: SAGE.
- Smith, J. A., Osborn, M. and Smith, J. (2003) 'Interpretative phenomenological analysis', *Qualitative psychology: A practical guide to research methods*, pp. 51-80.
- Smith, M. L. (1980) 'Publication bias and meta-analysis', *Evaluation in Education*, 4, pp. 22-24.
- Smith, S. C., Cano, S., Lamping, D. L., Staniszevska, S., Browne, J., Lewsey, J., van der Meulen, J., Cairns, J. and Black, N. (2005) 'Patient-Reported Outcome Measures (PROMs) for routine use in Treatment Centres: recommendations based on a review of the scientific evidence'.
- Smith, V., Clarke, M., Williamson, P. and Gargon, E. (2015) 'Survey of new 2007 and 2011 Cochrane reviews found 37% of prespecified outcomes not reported', *J Clin Epidemiol*, 68(3), pp. 237-45.
- Sollid, S. J., Lockey, D., Lossius, H. M. and group, P.-h. a. a. m. e. (2009) 'A consensus-based template for uniform reporting of data from pre-hospital advanced airway management', *Scand J Trauma Resusc Emerg Med*, 17, pp. 58.
- Staniszevska, S. 'GRIPP 2: Developing consensus on the reporting of patient and public involvement', *Involve Conference*.
- Staniszevska, S., Brett, J., Mockford, C. and Barber, R. (2011) 'The GRIPP checklist: strengthening the quality of patient and public involvement reporting in research', *Int J Technol Assess Health Care*, 27(4), pp. 391-9.

- Staniszewska, S., Haywood, K. L., Brett, J. and Tutton, L. (2012) 'Patient and public involvement in patient-reported outcome measures: evolution not revolution', *Patient*, 5(2), pp. 79-87.
- Stanley, K. (2007) 'Design of randomized controlled trials', *Circulation*, 115(9), pp. 1164-9.
- Starks, H. and Trinidad, S. B. (2007) 'Choose your method: a comparison of phenomenology, discourse analysis, and grounded theory', *Qual Health Res*, 17(10), pp. 1372-80.
- Stewart, D. W. and Shamdasani, P. N. (2014) *Focus groups: Theory and practice*. Sage publications.
- Streiner, D. L., Norman, G. R. and Cairney, J. (2014) *Health measurement scales: a practical guide to their development and use*. Oxford university press.
- Stucki, G., Boonen, A., Tugwell, P., Cieza, A. and Boers, M. (2007) 'The World Health Organisation International Classification of Functioning, Disability and Health: a conceptual model and interface for the OMERACT process', *J Rheumatol*, 34(3), pp. 600-6.
- Sunnerhagen, K. S., Johansson, O., Herlitz, J. and Grimby, G. (1996) 'Life after cardiac arrest; a retrospective study', *Resuscitation*, 31(2), pp. 135-140.
- Symmons, D. and Dawes, P. (1988) 'Summary and consensus view', *Br J Rheumatol*, 27(S1), pp. 76-7.
- Tallon, D., Chard, J. and Dieppe, P. (2000) 'Relation between agendas of the research community and the research consumer', *Lancet*, 355(9220), pp. 2037-40.
- Taylor, W. J. (2005) 'Preliminary identification of core domains for outcome studies in psoriatic arthritis using Delphi methods', *Ann Rheum Dis*, 64 Suppl 2, pp. ii110-2.
- Taylor, W. J., Schumacher, H. R., Baraf, H. S., Chapman, P., Stamp, L., Doherty, M., McQueen, F., Dalbeth, N., Schlesinger, N., Furst, D. E., Vazquez-Mellado, J., Mellado, J. V., Becker, M. A., Kavanaugh, A., Louthrenoo, W., Bardin, T., Khanna, D., Simon, L. S., Yamanaka, H., Choi, H. K., Zeng, X., Strand, V., Grainger, R., Clegg, D., Singh, J. A., Diaz-Torne, C., Boers, M., Gow, P. and Barskova, V. G. (2008) 'A modified Delphi exercise to determine the extent of consensus with OMERACT outcome domains for studies of acute and chronic gout', *Ann Rheum Dis*, 67(6), pp. 888-91.
- Tetzlaff, J. M., Moher, D. and Chan, A. W. (2012) 'Developing a guideline for clinical trial protocol content: Delphi consensus survey', *Trials*, 13, pp. 176.
- Tierney, S., O'Brien, K., Harman, N. L., Sharma, R. K., Madden, C. and Callery, P. (2015) 'Otitis media with effusion: experiences of children with cleft palate and their parents', *Cleft Palate Craniofac J*, 52(1), pp. 23-30.
- The Brain Resuscitation Clinical Trial II Study Group, (1991) 'A randomized clinical trial of calcium entry blocker administration to comatose survivors of cardiac arrest. Design, methods, and patient characteristics.', *Control Clin Trials*, 12(4), pp. 525-45

- Tong, A., Manns, B., Hemmelgarn, B., Wheeler, D. C., Tugwell, P., Winkelmayer, W. C., van Biesen, W., Crowe, S., Kerr, P. G., Polkinghorne, K. R., Howard, K., Pollock, C., Hawley, C. M., Johnson, D. W., McDonald, S. P., Gallagher, M. P., Urquhart-Secord, R., Craig, J. C. and Collaboration, S.-H. (2015) 'Standardised outcomes in nephrology - Haemodialysis (SONG-HD): study protocol for establishing a core outcome set in haemodialysis', *Trials*, 16, pp. 364.
- Tovey, D. (2010) 'The impact of Cochrane Reviews', *The Cochrane database of systematic reviews*, 2011, pp. ED000007-ED000007.
- Trzeciak, S., Jones, A. E., Kilgannon, J. H., Fuller, B. M., Roberts, B. W., Parrillo, J. E. and Farrar, J. T. (2009) 'Outcome measures utilized in clinical trials of interventions for post-cardiac arrest syndrome: a systematic review', *Resuscitation*, 80(6), pp. 617-23.
- Tufford, L. and Newman, P. (2012) 'Bracketing in qualitative research', *Qualitative Social Work*, 11(1), pp. 80-96.
- Tugwell, P. and Boers, M. (1993) 'OMERACT conference on outcome measures in rheumatoid arthritis clinical trials: introduction', *J Rheumatol*, 20(3), pp. 528-30.
- Tugwell, P., Boers, M., Brooks, P., Simon, L., Strand, V. and Idzerda, L. (2007) 'OMERACT: an international initiative to improve outcome measurement in rheumatology', *Trials*, 8, pp. 38.
- Turk, D. C., Dworkin, R. H., Allen, R. R., Bellamy, N., Brandenburg, N., Carr, D. B., Cleeland, C., Dionne, R., Farrar, J. T., Galer, B. S., Hewitt, D. J., Jadad, A. R., Katz, N. P., Kramer, L. D., Manning, D. C., McCormick, C. G., McDermott, M. P., McGrath, P., Quessy, S., Rappaport, B. A., Robinson, J. P., Royal, M. A., Simon, L., Stauffer, J. W., Stein, W., Tollett, J. and Witter, J. (2003) 'Core outcome domains for chronic pain clinical trials: IMMPACT recommendations', *Pain*, 106(3), pp. 337-45.
- van der Heijde, D., Bellamy, N., Calin, A., Dougados, M., Khan, M. A. and van der Linden, S. (1997) 'Preliminary core sets for endpoints in ankylosing spondylitis. Assessments in Ankylosing Spondylitis Working Group', *J Rheumatol*, 24(11), pp. 2225-9.
- Varni, J. W., Thompson, K. L. and Hanson, V. (1987) 'The Varni/Thompson Pediatric Pain Questionnaire. I. Chronic musculoskeletal pain in juvenile rheumatoid arthritis', *Pain*, 28(1), pp. 27-38.
- Wachelder, E. M., Moolaert, V. R., van Heugten, C., Verbunt, J. A., Bekkers, S. C. and Wade, D. T. (2009) 'Life after survival: long-term daily functioning and quality of life after an out-of-hospital cardiac arrest', *Resuscitation*, 80(5), pp. 517-22.
- Wagner, J. and Lee, S. (2014) 'Sampling Rare Populations', *Health Survey Methods*, pp. 77-104.
- Walker, J. (2010) 'The COMET initiative'. Available at: <http://blogs.bmj.com/bmj/2010/03/08/the-comet-initiative/> (Accessed 11 May 2013).
- Ward, D. J., Furber, C., Tierney, S. and Swallow, V. (2013) 'Using Framework Analysis in nursing research: a worked example', *J Adv Nurs*, 69(11), pp. 2423-31.

- Ware, J., Kosinski, M. and Keller, S. D. (1996) 'A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity', *Med Care*, 34(3), pp. 220-33.
- Ware, J. E. and Sherbourne, C. D. (1992) 'The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection', *Med Care*, 30(6), pp. 473-83.
- Warwick-Booth, L., Cross, R. and Lowcock, D. (2012) *Contemporary health studies: An introduction*. Polity.
- Waters, A. M., Tudur Smith, C., Young, B. and Jones, T. M. (2014) 'The CONSENSUS study: protocol for a mixed methods study to establish which outcomes should be included in a core outcome set for oropharyngeal cancer', *Trials*, 15, pp. 168.
- Whistance, R. N., Forsythe, R. O., McNair, A. G., Brookes, S. T., Avery, K. N., Pullyblank, A. M., Sylvester, P. A., Jayne, D. G., Jones, J. E., Brown, J., Coleman, M. G., Dutton, S. J., Hackett, R., Huxtable, R., Kennedy, R. H., Morton, D., Oliver, A., Russell, A., Thomas, M. G., Blazeby, J. M. and Group, C. O. a. i. S. i. S. S.-C. C. W. (2013) 'A systematic review of outcome reporting in colorectal cancer surgery', *Colorectal Dis*, 15(10), pp. e548-60.
- Whitehead, L., Perkins, G. D., Clarey, A. and Haywood, K. L. (2015) 'A systematic review of the outcomes reported in cardiac arrest clinical trials: The need for a core outcome set', *Resuscitation*, 88C, pp. 150-157.
- WHO 1946. Preamble to the constitution of the World Health Organization as adapted by the International Health Conference. New York.
- WHO 2001. International classification of functioning, disability and health (ICF). Geneva: World Health Organisation.
- Wiebe, S., Guyatt, G., Weaver, B., Matijevic, S. and Sidwell, C. (2003) 'Comparative responsiveness of generic and specific quality-of-life instruments', *J Clin Epidemiol*, 56(1), pp. 52-60.
- Williamson, P., Altman, D., Blazeby, J., Clarke, M. and Gargon, E. (2012a) 'Driving up the quality and relevance of research through the use of agreed core outcomes', *J Health Serv Res Policy*, 17(1), pp. 1-2.
- Williamson, P. R., Althma, D. G., Blazeby, J. M., Clarke, M. and Gargon, E. 2011. The COMET (Core Outcomes Measures in Effectiveness Trials) Initiative. *Trials*.
- Williamson, P. R., Altman, D. G., Blazeby, J. M., Clarke, M., Devane, D., Gargon, E. and Tugwell, P. (2012b) 'Developing core outcome sets for clinical trials: issues to consider', *Trials*, 13, pp. 132.
- Wilson, I. B. and Cleary, P. D. (1995) 'Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes', *JAMA*, 273(1), pp. 59-65.
- Wilson, J. T., Pettigrew, L. E. and Teasdale, G. M. (1998) 'Structured interviews for the Glasgow Outcome Scale and the extended Glasgow Outcome Scale: guidelines for their use', *J Neurotrauma*, 15(8), pp. 573-85.
- Wright, V. (1981) 'Do we need so many assays to detect suppression of inflammation', *Controversies in the Clinical Evaluation of Analgesic-Anti-inflammatory-Antirheumatic Drugs*. New York: FK Schattauer Verlag, 20.

<http://www.invo.org.uk/> (cited on 01.07.16).

- Wyer, S., Earll, L., Joseph, S., Harrison, J., Giles, M. and Johnston, M. (2001) 'Increasing attendance at a cardiac rehabilitation programme: an intervention study using the Theory of Planned Behaviour', *Coronary health care*, 5(3), pp. 154-159.
- Wylde, V., MacKichan, F., Bruce, J. and Gooberman-Hill, R. (2014) 'Assessment of chronic post-surgical pain after knee replacement: Development of a core outcome set', *Eur J Pain*.
- Young, B. and Bagley, H. (2016) 'Including patients in core outcome set development: issues to consider based on three workshops with around 100 international delegates', *Research Involvement and Engagement*, 2(1), pp. 1-13.
- Zigmond, A. S. and Snaith, R. P. (1983) 'The hospital anxiety and depression scale', *Acta Psychiatr Scand*, 67(6), pp. 361-70.
- Zochling, J., Sieper, J., van der Heijde, D., Braun, J. and Group, A. i. A. S. I. W. (2008) 'Development of a core set of domains for data collection in cohorts of patients with ankylosing spondylitis receiving anti-tumor necrosis factor-alpha therapy', *J Rheumatol*, 35(6), pp. 1079-82.

Appendices

Appendix 1.1: Utstein Resuscitation registry template: core and supplementary items

	System	Dispatch	Patient	Process	Outcome
Core	Population served Cardiac arrests attended Resuscitation attempted Resuscitation not attempted System description	Dispatcher identified cardiac arrest Dispatcher CPR instructions	Age Gender Witnessed arrest Arrest location Bystander CPR/AED First monitored rhythm Etiology	Response times Defibrillation time Target temp control Drugs Reperfusion attempted	Survived event Any ROSC 30-day survival/ survival to discharge Neurological outcome
Supplementary	DNAR legislation Termination of resuscitation rules Dispatch software used Resuscitation algorithms followed Data quality activities Prehospital ECG		Independent living Comorbidities Presence of STEMI Ventricular assist devices Cardioverter-defibrillator	Airway control type Number of shocks Drug timings CPR quality Vascular access type Mechanical CPR Targeted oxygenation/ventilation/ BP ECMO IAMP pH, lactate, glucose 12-lead ECG Neuroprognostication Hospital type/ volume	Transport to hospital Treatment withdrawal Cause of death Organ donation Patient reported outcome measures Quality of life measures 12-month survival

Appendix 3.1: Systematic review search strategy

1. (randomi?edadj control* adj trial*).mp. [mp=, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
2. Clinical trial*.mp.
3. exp Randomized Controlled Trials as Topic/
4. exp Clinical Trial/
5. exp Clinical Trials as Topic/
6. 1 or 2 or 3 or 4 or 5
7. Cardiac arrest.mp. or exp *Heart Arrest/
8. exp Cardiopulmonary Resuscitation/
9. cpr.mp.
10. (sudden adj5 cardiac death).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
11. Circulatory arrest.mp.
12. 7 or 8 or 9 or 10 or 11
13. 6 and 12
14. limit 13 to (english language and yr="2002 - 2012" and "all adult (19 plus years)")

Appendix 3.2: Systematic review data extraction table

Study number	1
Health domain	Process measure
Outcome	Time to defibrillation
Outcome measure	Time to defibrillation in VT/VF cardiac arrest
Details of how reported	Measured continuously in both groups
Reproducible	Yes
Intervention	Standard CPR vs Standard CPR and AECD monitoring
Comments	Utstein referenced
Time point	During resuscitation

Study number	1
Author	Ali et al
Title	Automated external cardioversion defibrillation monitoring in cardiac arrest: a randomized trial
Year	2008
Number of subjects	192
Location of arrest	In hospital

Appendix 4.1: Interview invitation letter



Point of contact: Laura Whitehead
Number: 0121 424 2647
Email: laura.whitehead@warwick.ac.uk
Research Degree Students,
Warwick Medical School,
University of Warwick,
Gibbet Hill,
Coventry
CV4 7AL

DATE

Dear **NAME**,

RE: Study (Identifying a core outcome set for cardiac arrest clinical trials)
We are writing to tell you about a study that is being run by the University of Warwick and Heart of England NHS Foundation Trust that involves survivors from cardiac arrest or their partners as participants.

We understand that some survivors from cardiac arrests may find it difficult to complete all the activities they were able to do before their arrest. If you do not feel well enough to participate in this study we would appreciate it if you could pass this information onto a partner that knows you well as we are also interested in speaking to them as part of our research.

The drive for completing this study is to make sure that the most appropriate and useful measurements are being reported in cardiac arrest clinical trials. Currently there is not a standardised approach to reporting which makes it very difficult when testing the effectiveness of different treatments. In addition to this currently what is reported is decided by clinicians and researchers, we want to include the patient view in this process as patients know which measurements mean the most.

After reading the information sheet enclosed please would you be able to contact us either by email, post or telephone to let us know if you are interested in taking part in this research. If you have any more questions about the study to help make a decision to participate please contact us (details are listed at the top of this letter.

Kind regards,

Laura Whitehead

Point of contact: Laura Whitehead
Number: 0121 424 2647 Email:
laura.whitehead@warwick.ac.uk
Research Degree Students,
Warwick Medical School,
University of Warwick,
Coventry,
CV4 7AL

Information sheet for potential participants: Identifying a core outcome set for cardiac arrest clinical trials

We are sending you this information because you or your partner was recently admitted to a hospital that is part of the Heart of England NHS Foundation Trust (Birmingham Heartlands Hospital, Solihull Hospital or Good Hope Hospital) after having a cardiac arrest (when the heart stops). This sheet provides you with some information about our study and how you can be involved.

What is the purpose of this study?

The purpose of this study is to make sure that the correct measurements are being recorded in cardiac arrest clinical trials and that these include the measurements patients feel are the most important. Currently in cardiac arrest research there are no guidelines in place for what should be measured in all trials. This means that a lot of different measurements are being recorded in trials making it difficult to compare the success of different treatments. In addition to this what is currently measured in trials to test treatments is decided by clinicians and researchers, we would like to get a patients input to this as you know what really matters to a cardiac arrest patient. This study is being conducted as part of a PhD.

Why have I been chosen?

You have been chosen to take part in this study because you have either experienced a cardiac arrest or someone close to you has. We feel that your experience can provide us with valuable information that clinicians and researchers may not have thought about before.

Do I have to take part?

It is not compulsory to take part and we will be extremely grateful if you would be interested in being a part of the study.

What will happen if I continue to take part?

Your involvement in the study will consist of a one off interview. If you express an interest to take part a PhD student (Laura) will be in contact with you to discuss the study and arrange a time and date to visit you. The interview will be carried out at your residence or a hospital based location. The interview will involve talking about your or your partner's life before and after your cardiac arrest in order to highlight any key areas of your health that were affected by the cardiac arrest. We anticipate

that the interview will last around 30 to 45 minutes. The interviews will be audio-recorded and transcribed.

What are the possible risks and benefits?

The disadvantage of this interview is that it will take up a modest amount of your time. You may also find it difficult when talking about your cardiac arrest, if you do find yourself getting upset the interview can be stopped at any point. There are no direct benefits of taking part in the research however this research has the potential to benefit future generations. If you have to make travel arrangements for your interview you will be reimbursed for these.

What happens if I have any questions, concerns or complaints about the research?

Please do not hesitate to contact the research team via telephone, email or letter (details are listed at the top of this letter). Complaints can be directed to Ms Jo Horsbrugh who is not a member of the direct research team. Contact details: telephone 024 7652 3716 Email: n.lynch@warwick.ac.uk Address: University of Warwick, Research Support Services, University House, Kirby Corner Road, Coventry, CV5 8UW.

Will my participation be confidential?

As soon as interviews have been transcribed the audio recording will be deleted. All transcripts will be given a random code and no names will be feature so none will be able to identify you from the transcripts. Only members of the research team will have access to any of your personal details and these will be stored on a password protected computer.

What will happen if I don't want to carry on with the study?

You are free to withdraw from the study at any stage. If you decide you don't want to take part in the study after your interview your data will not be included as part of our results.

What will happen to the results of the research?

The larger study is expected to be completed towards the end of 2015. The results will be published in a medical journal. If you would like a copy of the published results please let us know. Some of the results published may include examples of transcripts from interviews, but these will be given a random code and no names will be included so that you cannot be identified.

Who is organising and funding the study contact details?

The study is being organised by Laura Whitehead a PhD student at the University of Warwick. The study will be overseen by Dr Kirstie Haywood and Professor Gavin Perkins. The research will also be supported by the Academic Department of Anaesthesia, Critical Care, Pain and Resuscitation at Heartlands Hospital Birmingham. This study has been reviewed and approved by a NHS ethics committee. Currently this study is not receiving any external funding.

Please contact us via you post, email or telephone to confirm the details on the slip below if you are interested in taking part in the study. Likewise if you have any questions about the study before making a decision whether to participate please contact us for more information. We hope to hear from you soon.

Kind regards,

Laura Whitehead

Point of contact: Laura Whitehead
Number: 0121 424 2647 Email:
laura.whitehead@warwick.ac.uk
Research Degree Students,
Warwick Medical School,
University of Warwick,
Coventry,
CV4 7AL

Name:

I would like to be involved in the study:

Yes

☐

No

☐

Patient:

☐

Patient's partner:

☐

Contact details:

Address:

.....

Telephone number:

.....

Email address:

.....

Preferred method of contact:

.....

Signature:

.....



National Research Ethics Service

NRES Committee West Midlands - The Black Country

HRA NRES Centre Manchester
3rd Floor, Barlow House
4 Minshull Street
Manchester
M1 3DZ

Telephone: 0161 625 7821
Facsimile: 0161 625 7299

30 December 2013

Miss Laura Whitehead
PhD student
University of Warwick
Research Degree Students,
Warwick Medical School, University of Warwick
Coventry, Gibbet Hill
CV4 7AL

Dear Miss Whitehead

Study title: Identifying a Core Outcome Set for Cardiac Arrest
Clinical Trials
REC reference: 13/WM/0464
Protocol number: 1
IRAS project ID: 138348

Thank you for your letter of 24 December 2013. I can confirm the REC has received the documents listed below and that these comply with the approval conditions detailed in our letter dated 13 December 2013

Documents received

The documents received were as follows:

Document	Version	Date
Covering Letter		24 December 2013
Letter of invitation to participant	2	18 December 2013
Participant Consent Form	2	18 December 2013
Participant Information Sheet: Interviews	2	18 December 2013
Participant Information Sheet: Questionnaires	2	18 December 2013
Participant Information Sheet: Day Meeting	2	18 December 2013

Approved documents

The final list of approved documentation for the study is therefore as follows:

Document	Version	Date
Covering Letter		04 November 2013
Covering Letter		24 December 2013

Ethical approval letter

Page 2 of 2

Evidence of insurance or indemnity		06 August 2013
Interview Schedules/Topic Guides	Cardiac arrest patient interviews - 1	18 October 2013
Interview Schedules/Topic Guides	Cardiac arrest family members and carer interviews - 1	18 October 2013
Investigator CV	Laura Whitehead	
Investigator CV	Professor Gavin Perkins	18 October 2013
Investigator CV	Kirstie Haywood	
Letter from Sponsor		22 October 2013
Letter of invitation to participant	2	18 December 2013
Participant Consent Form	2	18 December 2013
Participant Information Sheet: Interviews	2	18 December 2013
Participant Information Sheet: Questionnaires	2	18 December 2013
Participant Information Sheet: Day Meeting	2	18 December 2013
Protocol	1	18 October 2013
REC application	3.5	05 November 2013

You should ensure that the sponsor has a copy of the final documentation for the study. It is the sponsor's responsibility to ensure that the documentation is made available to R&D offices at all participating sites.

13/WM/0464

Please quote this number on all correspondence

Yours sincerely



Miss Shehnaz Ishaq
REC Manager

E-mail: nrescommittee.westmidlands-blackcountry@nhs.net

Copy to: Dr Peter Hedges, Warwick University

Miss Tanzeem Begum, MIDRU Heartlands Hospital (Heart of England NHS Foundation Trust)

Dr Kirstie Haywood - K.L.Haywood@warwick.ac.uk

Professor Gavin Perkins - G.D.Perkins@warwick.ac.uk

Appendix 4.4: Interview consents form

Patient and partner consent form – Identifying a core outcome set for cardiac arrest clinical trials

Please initial each box and sign and date the bottom of the form:

- | | Initials |
|---|--------------------------|
| 1. I can confirm that I have read and understood the information sheet provided and have a copy to keep. I have had the opportunity to ask any questions about the study and understand why the research is being conducted | <input type="checkbox"/> |
| 2. I can confirm that I am aware that I have the right to leave this study at any point without my medical care or legal rights being affected. | <input type="checkbox"/> |
| 3. I am happy for this discussion to be audiotaped and transcribed. I understand that the transcription will be anonymised and the audio file will be deleted. I understand that direct quotes may be used but in a way where I will not be identified. | <input type="checkbox"/> |
| 4. I understand that the results of this study may be published in scientific journals or presented at scientific conferences. This information will be anonymised and I give permission for this. | <input type="checkbox"/> |
| 5. I understand that relevant data collected during the study, may be looked at individuals from the University of Warwick, from regulatory authorities or from the NHS trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to this data. I understand that my confidentiality is being protected in compliance with the Data Protection Act (1998). | <input type="checkbox"/> |
| 6. I agree to take part in this study. | <input type="checkbox"/> |

Participant name:
Date:

Signature:

Researcher name:
Date:

Signature:

Appendix 4.5: Topic guides

Topic guide for cardiac arrest patient interviews

This is a guide of topics to cover in interviews with cardiac arrest patients. There are example questions included for each topic area.

15. Topics:

1. Narrative
2. Pre-arrest
3. Post-arrest in hospital
4. Daily life and activities
5. Treatments management
6. Messages to others
7. Final questions/comments

16. Question examples:

1. Narrative
 - Could you tell me your story of your cardiac arrest?
2. Pre-arrest
 - Can you tell me about the days leading up to your cardiac arrest?
 - Can you tell me about your health leading up to your cardiac arrest?
 - Were there any signs of any problems with your health before your arrest?
 - What were you doing on the day of your cardiac arrest?
3. Post-arrest in hospital
 - Could you remember anything about the arrest?
 - Did experience any visions or out of body experiences?
 - Can you remember and describe how you felt when you woke up/regained consciousness?
 - Can you describe your time in hospital to me?
4. Daily life and activities
 - What has life been like since your cardiac arrest?
 - Where do you think you have made the most improvements since your cardiac arrest?
 - What effect has the cardiac arrest had on your daily life? Work, relationships?
 - Has your cardiac arrest restricted you in anyway? Have you had to make any changes to your daily routine?
 - What sort of activities have you been doing since your cardiac arrest?
 - Are there any activities that you are unable to do since your arrest?
 - Has the arrest had any effect on your social activities?

5. Treatment

- What treatment options have you discussed with your doctor? (ICD, pharmacological treatments)
- Do you have any side effects from any of the treatments you have that you have started because of your cardiac arrest?

6. Messages

- What do you think people that make decisions in the NHS need to know about the care for cardiac arrest patients?
- What do you think people that care for and complete research on cardiac arrest patients need to know about the experience that they may not understand?
- Do you have any messages that would be useful to others that have recently had a cardiac arrest?
- Do you have any messages that would be useful to the family of those that have recently had a cardiac arrest?

7. Final questions/comments?

- We have researched the end of our interview. Is there anything else you would like to add that we might have missed out?

Topic guide for cardiac arrest family member and carer interviews

This is a guide of topics to cover in interviews with cardiac arrest patients family member and carers. There are example questions included for each topic area.

17. Topics:

1. Narrative
2. Pre-arrest
3. Post-arrest in hospital
4. Daily life and activities
5. Treatments management
6. Messages to others
7. Final questions/comments

18. Question examples:

1. Narrative

- Could you tell me your story of their cardiac arrest?
- Tell me about what you were doing when the arrest happened?

2. Pre-arrest

- Can you tell me about the days leading up to their cardiac arrest?
- Can you tell me about their health leading up to their cardiac arrest?
- Were there any signs of any problems with their health before their arrest?
- What were you doing on the day of their cardiac arrest?

3. Post-arrest in hospital

- Can you tell me about when they were unconscious?
- Can you tell me about when they woke up/regained consciousness?
- Can you describe their time in hospital to me?

4. Daily life and activities

- What has life been like since their cardiac arrest?
 - Asking about changes to the patients and family members or carers life
- Where do you think they have made the most improvements since their cardiac arrest?
- What effect has the cardiac arrest had on daily life? Work, relationships?
 - Asking about changes to the patients and family members or carers life
- Has the cardiac arrest restricted you in anyway? Have you had to make any changes to your daily routine?
- Has the cardiac arrest made changes to their life? Have they had to make any changes to their daily routine?
- What sort of activities have they been doing since their cardiac arrest?
- Are there any activities that they are unable to do since their arrest?
- Do you think the cardiac arrest have affected their social activities?

5. Treatment

- Have you witnessed or been told about any side effects from any of the treatments that they have started because of their cardiac arrest?

6. Messages

- What do you think people that make decisions in the NHS need to know about the care for cardiac arrest patients?
- What do you think people that care for and complete research on cardiac arrest patients need to know about the experience that they may not understand?
- Do you have any messages that would be useful to the family of those that have recently had a cardiac arrest?

7. Final questions/comments?

- We have researched the end of our interview. Is there anything else you would like to add that we might have missed out?

Point of contact: Laura Whitehead

Number:.....

Email: laura.whitehead@warwick.ac.uk

Laura Whitehead,
Research Degree Students,
Warwick Medical School,
University of Warwick,
Gibbet Hill,
Coventry
CV4 7AL

Information sheet for potential participants: Identifying a core outcome set for cardiac arrest clinical trials

We are sending you this information because you or your partner were recently admitted to a hospital that is part of the Heart of England NHS Foundation Trust (Birmingham Heartlands Hospital, Solihull Hospital or Good Hope Hospital) after having a cardiac arrest (when the heart stops). This sheet provides you with some information about our study and how you can be involved.

What is the purpose of this study?

The purpose of this study is to make sure that the correct measurements are being recorded in cardiac arrest clinical trials and that these include the measurements patients feel are the most important. Currently in cardiac arrest research there are no guidelines in place for what should be measured in all trials. This means lots that a lot of different measurements are being recorded in trials making it difficult to compare the success of different treatments. In addition to this what is currently measured in trials to test treatments is decided by clinicians and researchers, we would like to get a patients input to this as they know what really matters to a cardiac arrest patient. This study is being conducted as part of a PhD.

Why have I been chosen?

You have been chosen to take part in this study because you have either experienced a cardiac arrest or someone close to you has. We feel that your experience can provide us with valuable information that clinicians and researchers may not have thought about before.

Do I have to take part?

It is not compulsory to take part and we will be extremely grateful if you would be interested in being a part of the study.

What will happen if I continue to take part?

Your involvement in the study will consist of three rounds of questionnaires that can be completed via post or online. If you express an interest to take part a PhD student (Laura) will provide you with the questionnaire via your method of preference. The questionnaire will ask you to give measurements that are taken in cardiac arrest care a score based on how important you think they are to you or your partner. We estimate that each questionnaire will take no longer than 15 minutes to complete. After each round of questionnaire the group results will be collected and anonymised and the mean results will be displayed with the next questionnaire. In the second questionnaire you can change your response if you like.

What are the possible risks and benefits?

The disadvantage of this process is that it will take up a modest amount of your time. There are no direct benefits of taking part in the research however this research has the potential to benefit future generations.

What happens if I have any questions, concerns or complaints about the research?

Please do not hesitate to contact the research team via telephone, email or letter (details are listed at the top of this letter). Complaints can be directed to Ms Jo Horsbrugh who is not a member of the direct research team. Contact details: telephone 024 7652 3716 Email: n.lynch@warwick.ac.uk Address: University of Warwick, Research Support Services, University House, Kirby Corner Road, Coventry, CV5 8UW.

Will my participation be confidential?

All results will be anonymised. Any results will be collectively represented as group results rather than any individual results. Only members of the research team will have access to any of your personal contact details and these will be stored securely.

What will happen if I don't want to carry on with the study?

You are free to withdraw from the study at any stage, however we would be grateful that you only choose to take part in the study if you are able to complete all three rounds of the questionnaire. If we do not have a high completion rate of all questionnaire rounds this can affect the quality of our results.

What will happen to the results of the research?

The larger study is expected to be completed towards the end of 2015. The results will be published in a medical journal. If you would like a copy of the published results please let us know.

Who is organising and funding the study contact details?

The study is being organised by Laura Whitehead a PhD student at the University of Warwick. The study will be overseen by Dr Kirstie Haywood and Professor Gavin Perkins. The research will also be supported by the Academic Department of Anaesthesia, Critical Care, Pain and Resuscitation. This study has been reviewed and approved by a NHS ethics committee. Currently this study is not receiving any external funding.

Please contact us via you post, email or telephone to confirm the details on the slip below if you are interested in taking part in the study. Likewise if you have any questions about the study before making a decision whether to participate please contact us for more information. We hope to hear from you soon.

Kind regards,

Laura Whitehead

Point of contact: Laura Whitehead

Number:.....

Email: laura.whitehead@warwick.ac.uk

Laura Whitehead,
Research Degree Students,
Warwick Medical School,
University of Warwick,
Gibbet Hill,
Coventry
CV4 7AL

Name:

I would like to be involved in the study: Yes ☐ No ☐

Patient: ☐ Patient's partner: ☐

Contact details:

Address:
.....

Telephone number:

Email address:

Preferred method of contact:

Signature:

Appendix 5.2 : Outcome framework table 1 of 4

Outcome	Examples provided in Healthcare professional and researcher survey	Examples provided in patient survey
<i>Pathophysiological manifestations</i>		
Circulatory function	<ul style="list-style-type: none"> • <i>During CPR: ETCO₂, coronary perfusion pressure, or the need for vasoactive drugs.</i> • <i>Immediately after CPR: the need for vasoactive drugs, further arrhythmia or blood pressure</i> • <i>During hospital stay: blood pressure or heart rate variability</i> 	How well the heart works and pumps blood around the body. For example heart rate and blood pressure
Brain function	<ul style="list-style-type: none"> • <i>During CPR: cerebral oximetry, carotid, blood flow or brain oxygenation</i> • <i>Immediately after CPR: MRI scan, EEG, biochemical markers of neurological status, seizure or level of consciousness</i> • <i>During hospital stay: biochemical markers of neurological status, mental capacity, level of consciousness, seizures or cognitive function.</i> • <i>At hospital discharge: cognitive function or level of consciousness</i> • <i>Within 1 year: cognitive function or level of consciousness</i> 	How well the brain works. This can affect the control of our muscles and some patients experience paralysis. This can also affect our memory, concentration and decision making. For example symptoms may include forgetfulness, difficulty finding the right words or being clumsier kidneys work.
Respiratory function	<ul style="list-style-type: none"> • <i>During CPR: intrathoracic pressures, arterial blood gas measurements or oxygen saturation</i> • <i>Immediately after CPR: duration on a ventilator oxygen levels or arterial blood gas results.</i> • <i>During hospital stay: duration on a ventilator, oxygen levels or breathlessness.</i> 	How well the breathing system works. For example the need for help with breathing or gas measurements
Renal function	<ul style="list-style-type: none"> • <i>The need for dialysis, kidney function tests or urine output.</i> 	How well other body parts work. For example how well the kidneys work.

Outcome framework table 2 of 4

Outcome	Examples provided in Healthcare professional and researcher survey	Examples provided in patient survey
<i>Survival</i>		
Survival	<ul style="list-style-type: none"> • <i>During CPR: any ROSC</i> • <i>Immediately after CPR: sustained ROSC, 4 hour survival or 24 hour survival</i> • <i>During hospital stay: survival to ICU discharge</i> • <i>Survival to hospital discharge</i> • <i>Within 1 year: at 3 months or</i> 	Survival
<i>Life impact</i>		
Physical symptoms	<ul style="list-style-type: none"> • <i>During hospital stay: loss of eye sight, ability to speak, loss of muscle strength, disrupted sleep and breathlessness</i> • <i>At hospital discharge: loss of eye sight, ability to speak, loss of muscle strength, disrupted sleep and breathlessness</i> • <i>Within 1 year: loss of eye sight, ability to speak, loss of muscle strength, disrupted sleep and breathlessness</i> 	Physical symptoms. For example: loss of eye sight, muscle weakness, poor sleep and breathlessness.
Fatigue	<i>Increased tiredness, feelings of exhaustion or tiredness for doing nothing. Note both physical and mental.</i>	Fatigue. For example increased feelings of tiredness and exhaustion. This may be from doing very little.
Activities of daily living (ADL)	<i>Being able to dress oneself, walking without support, washing oneself, doing housework and being able to drive</i>	Activities of daily living. For example being able to dress yourself, walking without support, washing and housework.
Emotional wellbeing	<i>Feelings of anxiety, feeling down or reduced confidence.</i>	Emotional well-being. For example feeling anxious, feeling down, reduced confidence or a loss of interest in hobbies.

Outcome framework table 3 of 4

Outcome	Examples provided in Healthcare professional and researcher survey	Examples provided in patient survey
<i>Life impact</i>		
Participation	<i>Being able to complete normal working or voluntary roles, carer roles, being able to do the same leisure activities (including sports) and being able to socialise like before.</i>	Being able to do what you want to do. For example: being able to return to employment, complete voluntary activities and being a carer. This also includes being able to do the same leisure activities (including sports) and being able to socialise like before.
Health Related Quality of life (HRQOL)	<i>The assessment of a patients' overall well-being that may have been impacted by a cardiac arrest, that is physical, social and emotional well-being</i>	Health related quality of life. By this we mean how well you feel overall physically, socially and emotionally.
Family impact	<i>Family members may experience stress and anxiety and there may be added pressure to relationships.</i>	The impact on the family. Sometimes having a cardiac arrest can also have an effect on people close to them. For example family members may have some stress and anxiety. It can also add pressure to relationships.
Adverse events and complications	<ul style="list-style-type: none"> • <i>During CPR: broken ribs</i> • <i>Immediately after CPR: broken ribs</i> • <i>During hospital stay: pneumonia or broken ribs</i> • <i>Within 1 year: side effects of medication or ICDs</i> 	Side effects. This includes any unexpected effects of treatment. For example: infection, broken ribs, scarring or side effects of tablets. Some patients may have monitors implanted that may cause side effects.

Outcome framework table 4 of 4

Outcome	Examples provided in Healthcare professional and researcher survey	Examples provided in patient survey
<i>Economic impact and resource use</i>		
Financial impact to the individual	N/A	After a cardiac arrest patients may have costs associated with the time off work or the need for more care and help.
Cost effectiveness of a intervention	N/A	By this we mean how much the benefits of an intervention outweigh the costs of the intervention
Duration of stay in intensive care	N/A	
Duration of stay in hospital	N/A	
Discharge location	N/A	Some patients may need more care after a cardiac arrest and may be discharged to a nursing facility.

Round 1: Individualised Feedback

Thank you for completing round 1 of the COSCA Delphi survey.

SUMMARY OF SCORES OF ITEMS WHERE IMPORTANCE REMAINS UNCLEAR:

Scores 1-3 indicate limited importance, 4-6 indicate important and 7-9 indicate critical importance to decision making.

During CPR	Group Median Score	Your score
Circulatory function	8	X
Brain function	7	X
Respiratory function	6	X
Renal function	3	X
Adverse effects	4	X

Immediately after CPR	Group Median Score	Your score
Brain function	7	X
Respiratory function	6	X
Renal function	5	X
Adverse effects	5	X

During Hospital stay	Group Median Score	Your score
Respiratory function	7	X
Renal function	7	X
Physical Symptoms	7	X
Fatigue	6	X
Activities of daily living	7	X
Emotional wellbeing	6	X
Health Related Quality of life	7	X
Family impact	6	X
Adverse effects	6	X

At hospital discharge	Group Median Score	Your score
Fatigue	6	X
Emotional wellbeing	7	X
Participation	7	X
Health Related Quality of life	7	X
Family impact	7	X

Within a year hospital discharge	Group Median Score	Your score
Fatigue	7	X
Emotional wellbeing	7	X
Participation	7	X
Family impact	7	X
Complications	7	X

SUMMARY OF CHANGES

Outcomes reaching consensus in Round 1:

Outcomes that reached consensus as critical outcomes during round 1 are described in the following survey. These will be taken forward and will not be considered further in round 2.

Additional outcomes:

Thank you for your comments and suggestions of outcomes that were missing from the survey. Some comments have helped expand the examples listed for outcome domains. The following outcomes have been added to the survey.

- Discharge location
- Cost effectiveness analysis
- The economic impact to an individual.
- Duration of stay in intensive care
- Duration of stay in hospital

As we are focussing on outcomes that assess patient outcome in larger clinical trials, therefore contextual factors (e.g. with healthcare professionals, family dynamics and risk factors) and process factors (e.g. time to defibrillation and CPR quality variables) have not been listed despite their importance and their influence on outcome. Organ donation is an important outcome for registry but has not been included for consideration for a core outcome set as this is not related to the outcome of the patient that would be in a cardiac arrest clinical trial.

Some comments referred to the outcome measurement that would be applied to assess certain outcomes. We would like to acknowledge this is an important issue and that for some of the outcomes listed there may not be currently appropriate assessment tools. However the purpose of this survey is to identify **what** to measure rather than **how** to measure which will be a further part of this research.

Appendix 5.3: Round 1 full results table 1 of 2

Outcome	Time point	Healthcare professionals and researchers scoring critical importance (n=99)	Patients and partners scoring critical importance (n=69)
Circulatory function	During CPR	51%	-
	Immediately after CPR	79%	-
	During hospital stay	70%	91%
Brain function	During CPR	53%	-
	Immediately after CPR	58%	-
	During hospital stay	87%	59%
	At hospital discharge	93%	57%
	Within 1 year	89%	83%
Respiratory function	During CPR	37%	-
	Immediately after CPR	64%	-
	During hospital stay	69%	73%
Renal function	During CPR	13%	-
	Immediately after CPR	28%	-
	During hospital stay	55%	67%
Survival	During CPR	86%	-
	Immediately after CPR	78%	-
	During hospital stay	87%	84%
	At hospital discharge	92%	88%
	Within 1 year	89%	89%

Appendix 5.4: Round 1 full results table 2 of 2 :

Outcome	Time point	Healthcare professionals and researchers scoring critical importance (n=99)	Patients and partners scoring critical importance (n=69)
Physical symptoms	During hospital stay	59%	53%
	At hospital discharge	81%	46%
	Within 1 year	83%	73%
Fatigue	During hospital stay	29%	41%
	At hospital discharge	42%	39%
	Within 1 year	57%	71%
Activities of daily living	During hospital stay	53%	22%
	At hospital discharge	73%	36%
	Within 1 year	77%	80%
Emotional wellbeing	During hospital stay	44%	44%
	At hospital discharge	61%	46%
	Within 1 year	65%	86%
Participation	At hospital discharge	61%	37%
	Within 1 year	68%	80%
Health related QoL	During hospital stay	53%	51%
	At hospital discharge	61%	42%
	Within 1 year	75%	90%
Family impact	During hospital stay	45%	65%
	At hospital discharge	52%	61%
	Within 1 year	62%	83%
Adverse events	During CPR	11%	-
	Immediately after CPR	18%	-
	During hospital stay	36%	39%
	Within 1 year	63%	71%

Appendix 6.1: Consensus meeting invitation



xxx/04/2015

Dear xxxx,

Thank-you for agreeing to attend the COSCA (Core Outcomes Set for Cardiac Arrest clinical trials) meeting in Prague on the afternoon of the **28th of October** and morning of the **29th of October**.

The purpose of the meeting is to discuss the outcomes that are the most important to cardiac arrest clinical trials and hence should be reported routinely as part of a core outcome set. At this meeting there will be healthcare professionals from an international background and patient representatives attending. In advance of the meeting we will circulate a reading pack with an overview of the study, a summary key findings to date and further information about the meeting.

The meeting will be held in advance of the European Resuscitation Council: Resuscitation 2015 The Guidelines Congress. The meeting will be held at the same location as the ERC congress: **The Prague Congress Centre** (5. Kvetna 65, 140 21 Prague 4, Czech Republic).

Please see below a preliminary itinerary:

Wednesday 28 th of October	
1pm – 5pm with refreshment break	Introductions and background to the study Group discussions and initial voting
Thursday 29 th of October	
9:30am-12:00 with refreshment break	Summary of findings from the day before Group discussions and final voting
Meeting close at 12:00 ahead of the ERC congress starting at 1pm	

We have a small budget to cover the costs of this meeting and are able to provide up to two nights hotel accommodation. We regret that we are unable to cover travel costs or costs of attending the ERC congress.

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Please do not hesitate to contact me if you have any questions and I look forward to meeting with you in Prague.

Kind regards,

Laura Whitehead, on behalf of the COSCA study group
Contact: Laura.Whitehead@warwick.ac.uk

Gavin Perkins, Vinay Nadkarni
Co-Chairs ILCOR

Supported by



Appendix 6.2: Pre-meeting information pack (format adapted for this thesis)

Background to the COSCA (Core Outcome Set for Cardiac Arrest clinical trials) Study Research in the field of resuscitation is crucial to improving survival rates and the outcome of cardiac arrest patients. The outcomes reported in research are important to the interpretation of study findings and understanding treatments. Outcomes can be assessed in a variety of ways and may include survival rates, pathophysiological manifestations and life impact as assessed by the physician or patient.

However, there is currently limited guidance for outcome reporting in cardiac arrest trials: outcome reporting lacks consistency and transparency, limiting data-syntheses conducted to best inform treatment recommendations (Moulaert et al., 2009, Elliott et al., 2011). Moreover, it is unclear whether the outcomes currently assessed have relevance to all key stakeholders, including patients.

Core outcome sets (COS) are increasingly recommended to improve the consistency and comparability of outcome reporting in clinical trials. A COS has been defined as:

“the minimum number of outcomes that should be measured and reported in all clinical trials, audits of practice or other forms of research for a specific condition,”

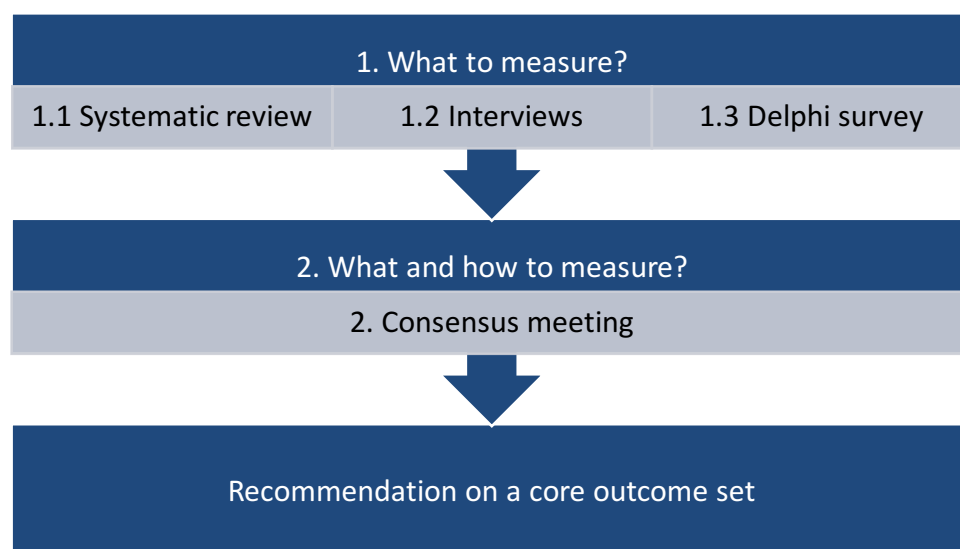
(www.COMET-initiative.com).

Typically a COS includes between 5 and 8 outcomes. However, a COS is not restrictive; rather, it represents the minimum number of outcomes that should be reported in trials for a particular condition. Additional, important outcomes can be included as determined by the trial.

Aim of the COSCA Study: To engage with the international resuscitation community to describe an agreed Core Outcome Set for Cardiac Arrest clinical trials, thus improving consistency and transparency in outcome reporting and benefitting future research in this field(Williamson et al., 2012a).

Developing a core outcome set: the COSCA approach

There are two key stages to the COSCA study, summarised in Figure 1.



Stage 1: What to measure?

Aim: To develop an in-depth understanding of what might be considered as core outcomes.

Three sub-studies were undertaken (and detailed below): Stages 1.1 (Systematic review of outcomes reported in cardiac arrest clinical trials) and 1.2 (Interviews with survivors of cardiac arrest and their partners) highlighted a large number of outcomes which could be considered for inclusion in a COS. During Stage 1.3 (International Delphi Survey of health professionals, researchers and patients) consensus on which of these outcomes were judged to be most important to decision-making was sought.

Stage 2: What and How to measure?

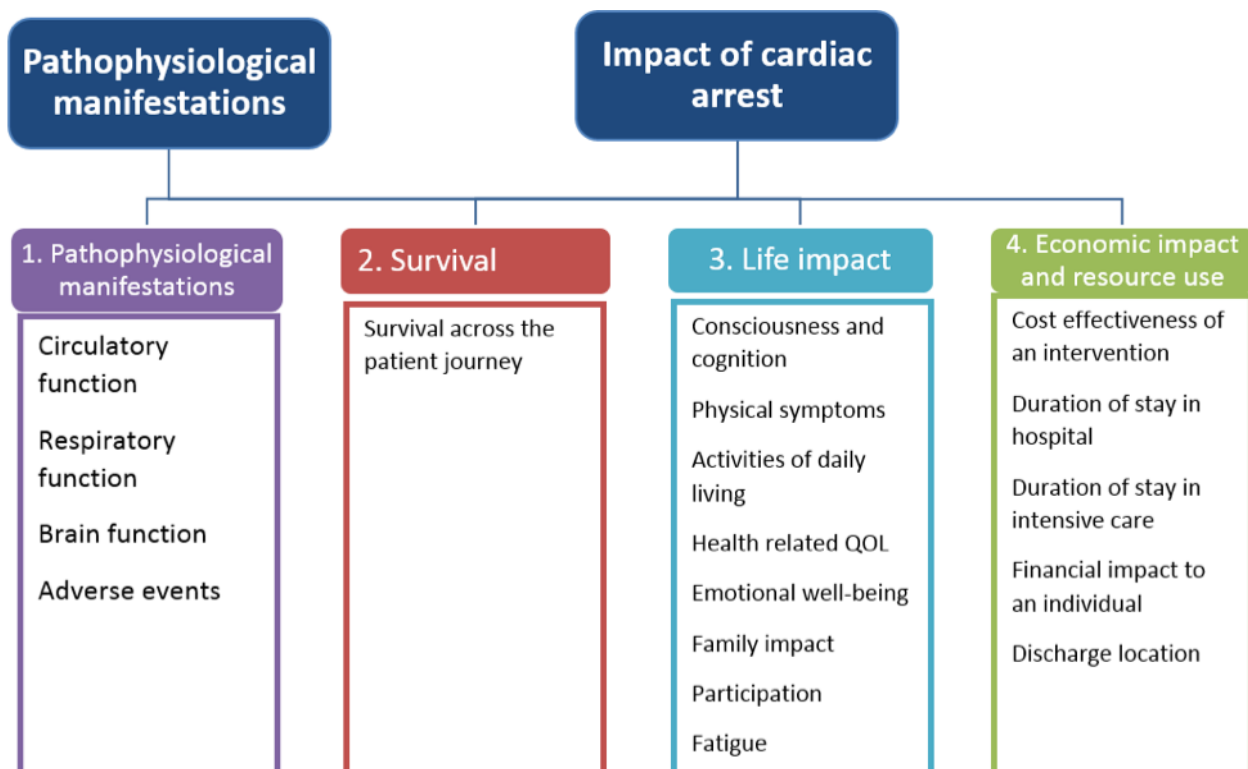
Aim: To reach consensus on which core outcomes should be included in the COS, and how best to measure them.

Achievement of this final aim will be the focus on the consensus meeting.

To support transparency in the process and consistency in the use of language, COSCA has adopted an established classification system, the OMERACT 2.0 filter (Boers et al., 2014c) to inform and guide COS development (Adapted version in figure 2). This classification system will be referred to throughout this document and during the consensus meeting.

Figure

1.1. Review of outcomes reported in cardiac arrest clinical trials (Whitehead et al, 2015(Whitehead et al., 2015)).



We completed a systematic review of cardiac arrest clinical trials to detail the range of outcomes currently reported (2002-2012) and which might be considered for inclusion in a future core outcome set. The wide heterogeneity and lack of transparency in reporting was highlighted.

Results: Across 61 randomised controlled trials over 160 different outcomes were identified. Reported outcomes were categorised across four core areas (including percentage of included studies reporting outcomes): survival (85.2%), life impact (52.5%), pathophysiological manifestations (41%) and processes of care (26.2%).

The patient's perspective was poorly assessed; no trial included an assessment of health related quality of life or social participation. Although 20 measures of life impact were described (functional status and neurological outcome) these were clinician-completed; only one was patient assessed.

Conclusions: Outcome reporting in cardiac arrest clinical trials lacks consistency and transparency. Guidance for improved outcome reporting is urgently required to reduce heterogeneity in outcome reporting, improve the quality of assessment in clinical trials, and to support the synthesis of trial data. The results highlight the need for a COS for cardiac arrest research to maximize the utility of future research.

Next steps:

The review provided a preliminary list of outcomes for consideration by participants in the International Delphi Survey (Stage 1.3).

Although highlighting the historically limited focus of clinical trials on patient-reported outcome assessment, this does not reflect the growing recognition within resuscitation science of seeking to better understand the perspective of survivors of cardiac arrest. Patient-reported outcomes and quality of life are now included as supplemental data elements in the most recent Utstein template detailed in appendix 1(Perkins et al., 2014). Therefore, Stage 1.2 was completed to improve our understanding of how survivors of cardiac arrest are affected.

Finally, outcomes reflecting 'processes of care' were not considered further. These outcomes were largely specific to the targeted intervention and hence had limited generalizability.

1.2. Interviews with cardiac arrest survivors and their partners:

We interviewed survivors of cardiac arrest and their partners' to improve our understanding of how their lives had been affected by the cardiac arrest, how they were feeling now, and what they can and cannot do. We sought to understand the outcomes that people care most about when seeking treatment or recovering from the arrest, including functional and emotional changes and their ability to live normal, productive lives.

Results: Semi-structured interviews were conducted with 8 survivors (41-79 aged (63 mean), 3 females and 5 male) and three of their partners between 3 and 12 months post-hospital discharge. The results highlighted survival and life impact as the most important

core areas. Outcomes included: **survival, physical symptoms, emotional well-being, social well-being and participation, and the impact to others**. Table 1 describes examples of the symptoms and their further impact contributing to these themes.

Table 1: Interview themes identified from interviews and further examples of these themes.

Themes	Examples
Survival	Gratitude to survive and recognizing the seriousness of the event.
Physical symptoms	Cognitive function (memory, decision making and linguistic skills), breathlessness, muscle strength, side effects (impaired vision, rib break, ICD complications), fatigue, activities of daily living and increased dependence.
Emotional well-being	Low self-esteem, low confidence, depressive symptoms, anxiety and increased frustrations.
Social well-being and participation	Employment, carer roles, socialization and the ability to do hobbies.
Impact to others	Increased work, stress and worry and strains on relationships.

Conclusion: The interviews were instrumental in developing our understanding of the wide-ranging and significant impact of cardiac arrest on the individual. A large number of outcomes, largely reflecting the significant life impact of cardiac arrest, were described. Crucially, several of these including; aspects of physical function, emotional well-being, social well-being and the impact to others have not historically been reported in cardiac arrest RCTs. An individual's pre-arrest status is a gold standard against which they judge their current health status.

The interviews provided important additional information pertaining to the life impact of cardiac arrest, and hence outcomes which should be considered for inclusion in the COS.

2. Summary of Stages 1.1 and 1.2:

Stages 1.1 and 1.2 informed the development of a framework of possible outcomes for inclusion in a future cardiac arrest core outcome set. This framework was used to inform the development of a survey questionnaire for Stage 1.3: an international Delphi survey with health professionals, researchers, patients and their partners.

2.1. International Delphi Survey

Methods: We conducted a 2-stage on-line Delphi survey with an international group of healthcare professionals, researchers, patients and their partners'. To enhance acceptability, separate questionnaires were developed for 1) the healthcare professionals and researchers, and 2) the patients and patient's partners. Questionnaires focused on the same central themes, but utilized language and terminology deemed to be acceptable to each group. The results from each group were kept separate throughout the process.

The questionnaires were developed and piloted with representatives from both groups, this indicated that the time point of assessment was an important factor when considering

what should be assessed. Therefore, outcomes were listed across the patient journey at the following time points: 1) during CPR; 2) immediately after CPR; 3) during hospital stay; 4) at hospital discharge; and 5) within 1 year. Informed by discussion with patients and their recall of the period following cardiac arrest, patients were not asked about the importance of outcomes during and immediately after CPR.

All outcomes included in the Delphi survey, and associated definitions and examples, are provided in appendix 2.

Round 1: 44 outcomes were listed in the healthcare professional and researcher survey and 32 patient and partner survey. Participants rated each outcome (outcome domain) on a 9 point GRADE Scale with 1-3 indicating limited importance; 4-6 important but not critical and 7-9 indicating critical importance to decision making.

Outcomes reaching critical importance (defined as >70% of participants scoring the outcome as critically important (scores 7-9) and <15% of participants scoring the outcome as of limited importance (scores 1-3)) were highlighted and listed for further consideration during the proposed consensus meeting. These outcomes were not considered further during the Delphi process. However, additional outcomes suggested in round 1 were introduced in round 2.

The results from round 1 highlighted that most participants judged most outcomes as important to their decision-making; many outcomes indicated importance but didn't reach a high level of consensus of critical importance. Therefore, to facilitate discrimination between the remaining outcomes (which were judged as important in round 1), and a reduction in number of outcomes that could be considered further for inclusion in the COS, in round 2 participants were invited to 'rank' the most important outcomes.

Round 2: Healthcare professionals and researchers received a shortened list of 33 outcomes and were invited to rank order their top 10 outcomes in order of importance for decision making. Patients and partners received a shortened list of 22 outcomes and were invited to rank their top 5 outcomes only.

Results:

Round 1: 99 healthcare professionals and researchers and 69 patients and partners from 15 different countries completed round 1. A high level of consensus of critical importance to clinical decision-making was achieved for 15/44 outcomes considered by the health professionals and researchers during round 1. A high level of consensus of critical importance was achieved for 14/32 outcomes considered by the patients and partners during round 1. Five 'new' outcomes were added as a result of suggestions in round 1.

Round 2: There were acceptable completion rates for both health professional and researcher (57.3%) and patient and partner (63.2%) groups in round 2. Consensus criteria was set as >70% of participants including the outcome in their top 10 (or 5) ranking. Items close to consensus (>60% of participants including the outcome in their ranking) were also highlighted for further consideration during the consensus meeting.

Number of outcomes to be considered during consensus meeting:

A total number of 27/44 outcomes across all core areas and all time-points reached the high levels of consensus (or borderline consensus) defined for rounds 1 and 2 of the Delphi

(Table 2): 7 pathophysiological manifestations; 5 survival and 15 life impact. These outcomes will be the focus of the consensus meeting.

There were important similarities and discrepancies between both groups: results are therefore presented separately. The healthcare professional and researcher group reached consensus on 21/27 outcomes (Table 2 health professional scores indicated by circles) and the patient and partner group reached consensus on 18/27 outcomes across core areas (Table 2: patient scores indicated by triangles).

Both groups achieved consensus on a total of 10/27 outcomes: Circulatory function during hospital stay, survival during hospital stay, survival at hospital discharge and consciousness and cognition at hospital discharge. Survival, consciousness and cognition, physical symptoms, activities of daily living, health related quality of life and participation all within 1 year.

A major difference between groups was the assessment of fatigue. Consensus within the patient group highlighted the critical importance of assessing fatigue within 1 year. By contrast, consensus within the healthcare professional group designated fatigue assessment as being of limited importance.

11/33 and 7/22 outcomes listed in round 2 were judged to have limited importance for both healthcare and patient groups respectively (<15% included the outcome in their ranking).

Economic and resource use: Although outcomes considered within this core area did not reach consensus during the Delphi process, this important area will be considered further during the consensus meeting. Five potential outcomes within this core area and time-points at which such an assessment may be most important are listed in Table 2; this creates up to 10 additional outcomes for further consideration.

Table 2: Outcomes reaching consensus after two rounds of Delphi survey

Core Area	Outcome domain	During CPR	Immediate after CPR	During hospital discharge	At hospital discharge	Within 1 year
Pathophysiological manifestations	Circulatory function	○	●	●▲		
	Respiratory function			▲		
	Renal function					
	Brain function (neurological markers)		○	○▲		
	Adverse events					▲
Survival	Survival	●	●	●▲	●▲	●▲
Life impact	Consciousness and cognition		○	○▲	●▲	●▲
	Physical symptoms*				●	●▲
	Activities of daily living				●	●▲
	Health related quality of life				○	●▲
	Emotional well-being					▲
	Family impact					▲
	Participation				△	●▲
	Fatigue					▲
Economic impact and resource use	Cost effectiveness					
	Duration of stay in hospital					
	Duration of stay in intensive care					
	Financial impact to an individual and family					
	Discharge location					

Key:

- Note Outcomes greyed out were not scored on their importance at these time points. Healthcare professional and researcher group consensus (>70% scores 7-9 R1 or >70% ranking in R2)
- ▲ Patient and partner consensus (>70% 7-9 R1 or >70% ranking in R2)
- Healthcare professional and researcher group close to consensus (>60% ranking in R2)
- △ Patient and partner close to consensus (>60% ranking in R2)

Foot note: * Physical symptoms' refers to 'Loss of eye sight, ability to speak, loss of muscle strength, disrupted sleep and breathlessness.'

3. Stage 2: WHAT and HOW to measure?

4. COSCA international consensus meeting

Results of the international Delphi survey described consensus of critical importance for 22 outcomes across three core areas: survival, pathophysiological manifestations and life impact. A further 5 outcomes reached a high level of consensus of critical importance and will be considered further during the consensus meeting.

Although not reaching consensus during the Delhi survey, up to ten additional outcomes which reflect economic impact and resource use will also be considered further during the consensus meeting. It is acknowledged that relevant stakeholders such as funders, healthcare commissioners and healthcare managers have been absent from the COS development process to date.

Combined, this provides a total of 37 outcomes across the patient journey, which must be considered for inclusion in the proposed COS. This is clearly too many. Informed by good practice guidance for COS development, we seek to define a minimum number of outcomes - ***a maximum of between 5 and 8 across all core areas and time-points***, which must be included in all future cardiac arrest clinical trials.

Further exploration of the short-listed outcomes is required to drive development of the final COS.

The COSCA international consensus meeting will bring together international experts in the field of cardiac arrest research and patient representatives, to discuss the results of the COSCA process and to achieve a final consensus on a short-list of outcomes.

Meeting aims

Day 1: By the end of day 1:

- We will produce a shortlist of **up to 7 outcomes to include as part of a core outcome set**. This short-list will summarise both **WHAT to measure and WHEN to measure** (broad time points).

Day 2: By the end of day 2:

- We will reach consensus on **HOW to measure these outcomes** (including focused time points).

Overall aim:

To define a core set of no more than 7 outcomes that should be reported routinely across cardiac arrest clinical trials, detailing when and how to report the selected outcomes.

Meeting structure

We have a lot to achieve over the two-days; the timetable is very busy! Please aim to be timely in your arrival and ready to contribute.

Day 1: What and When to measure? Exploring core areas and associated outcomes

Day 1 will include a plenary presentation of the research completed to date, and both small and large group discussions before participants are invited to vote on 'what' and 'when' to measure.

Following the plenary presentation, attendees will be assigned to four small groups. Each group will include health professionals, researchers, and a patient representative. Each group will independently explore the **four core areas described within the classification framework: 1) Pathophysiological manifestations, 2) Survival, 3) Life impact and 4) Economic impact and resource use**. Each core area will have a named facilitator who will support the small group discussions, feeding back the results from each small group discussion on the specific topic.

A named note-taker will take detailed notes of each group discussion. Participants will be invited to write key thoughts on sticky-notes which will contribute to the developing discussion. Discussions will focus on WHAT to measure: which outcomes within each core area are most important; and WHEN, if important, they should be assessed. It is anticipated that discussions will also consider 'how' important outcomes could be assessed; but this final point will be returned to on day 2.

Following the small group discussions, all groups will reconvene. The facilitators will feedback the key findings from the small group discussions. There will then be an opportunity for a large group discussion of any key issues or discrepancies that may have arisen in advance of the group being invited to vote on both 'WHAT' and 'WHEN' measure.

Day 1 will close with voting to select the outcomes to be included as part of the core outcome set.

Day 2: How and When to measure? Exploring how to measure outcomes included as part of a core outcome set.

Day 2 will begin with a summary of the findings from day 1. Similarly to day 1 breakout discussions will take place, this time focussing on '**how**' to assess selected outcomes. As part of this discussion more focussed time points of assessment will also be discussed in further detail.

Limited evidence is available to inform the question of 'how' to measure; the discussions will be largely informed by the experience and opinion of gathered participants. Please bring to the meeting any evidence that you think will help inform the discussion of 'how' to measure outcomes selected as part of a core outcome set.

Table 3: Meeting timetable (Subject to change)

Day 1 12:00 :1700 Holiday Inn Prague Congress Centre Meeting room D	
12:00- 12:30	Registration and light lunch
12:30- 13:00	Welcome and introductions
13:00-13:20	Background to the COSCA study and meeting structure
13:20-14:00	Breakout group discussion 1: What to measure and when?
14:00-14:35	Breakout group discussion 2: What to measure and when?
14:35-14:45	Break (Light refreshments)
14:45-15:20	Breakout group discussion 3: What to measure and when?
15:20-15:55	Breakout group discussion 4: What to measure and when?
15:55-17:00	Feedback and voting on what and when to measure. Further discussion and close.
19:00 Evening drinks	
Day 2 8:00 -12:00 Holiday Inn Prague Congress Centre Meeting room D	
8:00-8:20	Welcome – Reminder of yesterday’s discussion and voting
8:20-8:55	Breakout group discussion 1- How and when to measure?
8:55-9:30	Breakout group discussion 2 – How and when to measure?
9:30-10:05	Breakout group discussion 3– How and when to measure?
10:05-10:15	Break (Light refreshments)
10:15-10:40	Breakout group discussion 4 – How and when to measure?
10:40-11:20	Group feedback on how and when to measure.
11:20-11:45	Final voting.
11:45-12:00	Discussion and further steps.
12:00	Light lunch(Esprit Restaurant) before the ERC Congress starts at 1pm.

Meeting attendees:

Chair and facilitators (non-voting attendees): Vinay Nadkarni, Gavin Perkins, Kirstie Haywood, Michael Smyth, F

Group A:	Group B:	Group C:	Group D:
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We would very much like to thank you for your interest in the study and making arrangements to join us on the 28th-29th of October. It promises to be a busy, stimulating and enjoyable meeting – bringing together a wide range of expertise and experience from patients, patient representatives, clinicians and researchers.

If you have any queries please do not hesitate to contact the team on:
laura.whitehead@warwick.ac.uk

We look forward to seeing you in Prague,

E-Signature

Laura Whitehead, on behalf of the COSCA team.

Acknowledgments

We would like to thank: Laerdal for their assistance funding this meeting, the support and help of ILCOR and the ERC for recruitment in the Delphi stages, participants across this stu

References

Appendix 6.3 Voting form template

Core Area	Outcome domain	During CPR	Immediately after CPR	During hospital stay	At hospital discharge	Within 1 year
	Circulatory function	○	●	●▲		
	Respiratory function			▲		
	Renal function					
	Brain function (neurological markers)		○	○▲		
	Adverse events					▲
Survival	Survival	●	●	●▲	●▲	●▲
	Consciousness and cognition		○	○▲	●▲	●▲
	Physical symptoms				●	●▲
	Activities of daily living				●	●▲
	Health related quality of life				○	●▲
	Emotional well-being					▲
	Family impact					▲
	Participation				△	●▲
	Fatigue					▲
Economic impact and resource use	Cost effectiveness					
	Duration of stay in hospital					
	Duration of stay in intensive care					
	Financial impact to an individual and family					
	Discharge location					

- Key: Note Outcome domains greyed out were not scored on their importance at these time points.
 Healthcare professional and researcher group consensus (>70% scores 7-9 R1 or >70% ranking in R2)
 ▲ Patient and partner consensus (>70% 7-9 R1 or >70% ranking in R2)
 ○ Healthcare professional and researcher group close to consensus (>60% ranking in R2)
 △ Patient and partner close to consensus (>60% ranking in R2)

Core Area	Outcome domain	During CPR	Immediately after CPR	During hospital stay	At hospital discharge	Within 1 year
Pathophysiological manifestations	Circulatory function					
	Respiratory function					
	Renal function					
	Brain function (neurological markers)					
	Adverse events					
Survival	Survival					
Life impact	Consciousness and cognition					
	Physical symptoms					
	Activities of daily living					
	Health related quality of life					
	Emotional well-being					
	Family impact					
	Participation					
	Fatigue					
Economic impact and resource use	Cost effectiveness					
	Duration of stay in hospital					
	Duration of stay in intensive care					
	Financial impact to an individual and family					
	Discharge location					

Note patients and partners were not asked about the importance of outcomes during CPR or immediately after CPR.

You will be asked to score up to 7 outcomes for core outcome set inclusion from those with the white boxes.